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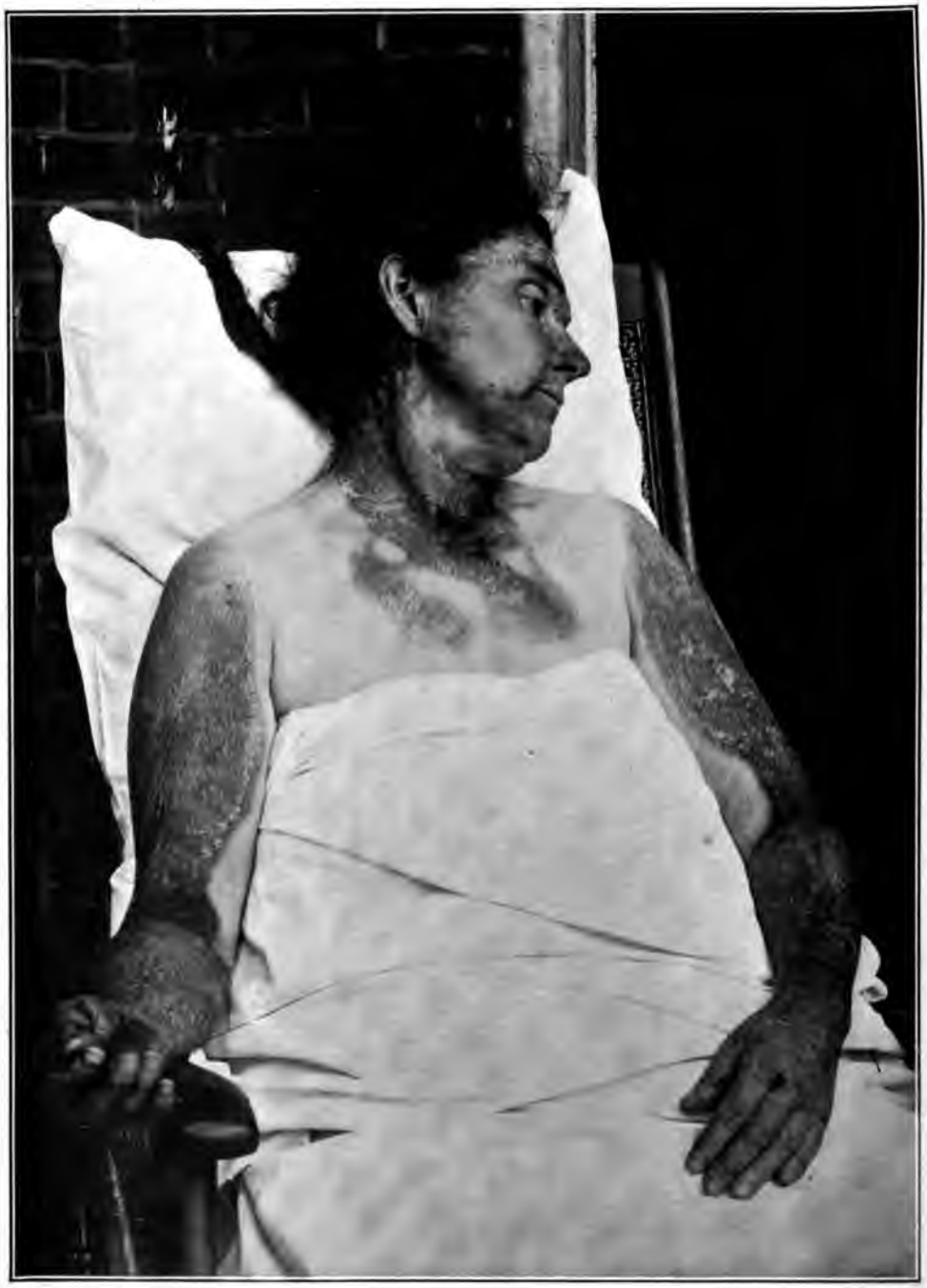

PELLAGRA

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PELLAGRA

By
H. F. Harris, M. D.
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TO THE MEMORY OF THOSE MASTER PELLAGROLOGISTS,

GAETANO STRAMBIO (SR.)

AND

MICHAEL GHERARDINI,

WHOSE UNSURPASSED GENIUS EXCITE EQUALLY

OUR WONDER AND ADMIRATION,

THIS VOLUME IS DEDICATED BY THE

AUTHOR

PREFACE

When just seventeen years ago the author's attention was first particularly directed to pellagra, he was at once struck with the fact that but little attention had been paid to this disease by English wrtiers. Further investigation quickly showed, however, that there is an enormous foreign literature on the subject—in the main Italian—extending backward for almost two centuries.

Notwithstanding the great number of articles that have been written on pellagra, a careful inquiry likewise developed the fact that no work aiming at being complete and systematic has appeared on this disease since the publication of Lombroso's well-known treatise in 1892. It is true that this book was translated into German, with some additions, by Kurella in 1898, but even this revised and in some directions enlarged edition of the work by no means included all of value that had been written on the subject.

The same criticism applies to the brochure of Marie, published in 1908, which in effect is nothing more than a somewhat abbreviated French translation of Lombroso's treatise.

Finding, then, that there was no systematic work that included the results of more modern investigation on pellagra, the author began collecting material with the idea of ultimately writing a monograph that would supply a complete exposition of the knowledge which has so far been obtained upon the subject. It was felt that in order that this object might be achieved it would be highly desirable to secure the writings of both the earlier and more recent investigators, and, although these were not in all instances obtainable, it is scarcely an exaggeration to say that this has been in effect accomplished. Wherever this was possible papers of value on this subject have been carefully read, and abstracts made of everything they contained that seemed important—a task of no small difficulty. That the best judgment has been at all times displayed in the selection of material could not be claimed, and it may be true that there are instances in which opinions, and even the results of investigations, might as well have been omitted. On the other hand it may also be the case that some writers have received inadequate attention, but if this be true, the error has been unintentional. Inasmuch as the author's principal object in writing this monograph was to make accessible to the English reader as complete a résumé as possible of the foreign literature on pellagra, it was early recognized that if this hope was to be realized the limits of the volume would forbid anything more than a most cursory reference to the many excellent papers on this subject that have appeared in this country, and he has been, therefore, constrained to cite briefly the results only of such investigators as appeared to contain matter of exceptional interest.

In collecting material for a history of our knowledge of pellagra, the author was early struck with the fact that there seems a general disposition in many quarters to imagine that the etiologic studies of this disease have been limited in the past to the maize theory, but it was quickly found that this conception is wholly erroneous, and that of the perfect flood of theories recently put forward scarcely one is fundamentally new.

It was likewise found that from a symptomatological standpoint everything of importance concerning this malady has long been known, and that in this direction we have in recent years made little or no real progress.

The author would call the attention of the reader to the fact that in so far as was possible he has attempted to review in historical order the various articles and papers that have appeared on pellagra, and in following out this idea has been compelled to record chronologically the names of the more prominent writers on this disease. He would particularly stress the fact that these names are not mentioned with the idea of proving by weight of numbers or authority the various theories with which they are associated, but that they are rather referred to for the purpose of giving proper credit, and to trace in sequence the various views that have been gradually developed on this subject.

These remarks can not be brought to a close without an expression of the author's profound gratitude to the Georgia State Board of Health, not only for having given him permission to investigate this subject, but for its uniformly kind and generous support, without which the work could not have been done. It is furthermore impossible to speak too highly of the aid given by Mr. C. Louis Tinsley, clerk of the Board, whose patient and most intelligent assistance has been simply invaluable.

The author also wishes to express his deep appreciation of the remarkable paper on Indian corn, which will be found in the appendix, by Prof. P. O. Vanatter, Superintendent of Field Demonstrations, of the State College of Agriculture, which is certainly not the least valuable part of the work.

He further desires to thank Dr. B. M. Cline, of the State Sanitarium for the Insane, and Dr. T. F. Abercrombie, City Health Officer of Brunswick and later Secretary of the Georgia State Board of Health, for their kindness in sending him pathological materials.

The writer would also express his high appreciation of the work of Mr. Frank L. Henry, from whose beautiful drawings the illustrations of this volume were copied.

In conclusion the author would distinctly disclaim for this volume any pretense of originality; if he has at times criticised, or attempted to co-ordinate and sum up the results of the investigations of others, he has consistently endeavored to state only what the facts seemed to warrant, and has been actuated wholly by a desire to arrive at the truth, and to aid those who may be interested in this subject.

H. F. H.

ATLANTA, GA., March 10, 1919.

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PELLAGRA

CHAPTER I

When Casal, about the year 1730, first began his observations on the malady now universally known as pellagra the affection had evidently existed for some time in the northwestern provinces of Spain, and had already received from the peasantry the name of *mal de la rosa* (disease of the rose), by which he described it.

It is equally certain that pellagra (rough skin) was by no means a new affection when it was many years later discovered by Frapolli in Italy; he likewise admits that the name by which he described the disease—spelled by him *pelagra*— was of popular origin, and that this was the appellation by which it was generally known to the dwellers of the country districts among whom it occurred. Some writers have asserted that this term is of Greek origin, while others have assumed that it came directly from the Latin; since, as has just been remarked, it was first employed by the peasants of northern Italy, it would seem that there could be no doubt whatever that it is derived from the Italian words *pella,* skin, and *agra,* unsightly, rough.

As the disease disseminated itself throughout the maize-eating provinces of southern Europe it was called by a great variety of names among the different peoples who fell a prey to it, a partial list of which now follows:

SPANISH.—*Mal de la rosa, mal* or *enfermedad del higado, flema salada, mal del monte, mal roxo,* and *mal da Asturias.*

ITALIAN.—*Scorbuto alpino, pellarella, pellarina, raffania maistica, paralysis scorbutica, georgopathia, colica di primavera, mal rosso, risipola Lombarda, mal della milza, mal della spienza, colore del fegato, scottatura solare, insolato di primavera, mal della miseria, scottatura di sole, lepra italica, psychoneurosis maidica, maidismus, salso, mal del padrone, balordone, risipola estiva, elephantiasis italica, lebbra* or *rosa delle Asturie.*

FRENCH.—*Gale de Saint-Ignace, mal de la Teste, gale de Saint-Agnan, pelade, éruption de Lombardie, mal des Saintes-Mains, mal de Sainte-Rose.*

ROUMANIAN.—*Pâr le alà, jupiualà, buba trânjilor, rana trânjilor.*

AUSTRO-HUNGARIAN.—As the name by which the disease is now quite universally known was generally adopted before the malady became epidemic in Austro-Hungary it seems that it was there always called pellagra.

RUSSIAN.—The disease is here also called pellagra.

HISTORY, AND BRIEF RESUME OF THE MORE IMPORTANT EARLY PAPERS THAT APPEARED ON PELLAGRA.

We have, unfortunately, no certain knowledge as to either the precise period when pellagra first made its appearance, or in what part of the world its terrible ravages began.

It is thought by some that this affection in all likelihood existed in the new world at a period that far antedated its discovery in Spain—this view having been particularly upheld by those who are advocates of the theory that it is caused by the habitual consumption of Indian corn. It is pointed out by such writers that the native population, particularly of Mexico, at the time of the conquest, subsisted largely or even almost entirely on this cereal, and that, if their assumptions are correct as to its method of production, it could hardly be doubted that the disease must have prevailed in these regions for an indefinite period in the past. Quite irrespective of such theoretical considerations, we are in possession of certain data which make this view not improbable. For example, it is well-known, and not without significance in this connection, that many of the early Spanish writers mentioned that the natives lacked the bodily vigor of their European conquerors, and were on the whole small and of feeble constitution. Of some importance also is the fact, referred to by Vales in his most excellent monograph on pellagra in Yucatan, that the different Indian tribes each has its own peculiar name for this disease—this being regarded as evidence of the antiquity of the affection. We should not, however, jump to the conclusion, without proper investigation, that the eating of maize in Mexico necessarily implied a concomitant pellagra, since, as was first clearly shown by the great Italian chemist, Selmi, the previous boiling of the maize seeds in lime water or other alkaline solution—which is a universal practice among these people when preparing it for food—in all likelihood robs the grain, to a great extent or entirely, of those poisonous substances which all who have in modern times investigated the subject agree are constantly present in this cereal, and which have been generally thought to be the pellagrogenic agencies.

It should also be remembered that in case we go back to the old view—almost universally held by the pellagrologists of the first half of the last century—that pellagra is the result of an insufficient or badly balanced diet, it would *a priori* appear as extremely likely that the affection prevailed in the regions just referred to, since it is a well-established fact that maize is an imperfect food, and would be likely followed by disastrous results in case it be employed as the basis for the dietary of any people for generation after generation.

As regards the development of pellagra in Europe, it may be confidently asserted that the disease made its appearance early in the eighteenth century, it having been first observed about 1730 by Casal in the province of Asturia, in northwestern Spain. However, this writer did not immediately publish the results of his labors, and, indeed, made no record of them until about five years later. Even

after his treatise on the subject was completed, Casal, with an easy indifference characteristic of the age, suffered his manuscripts to remain unpublished throughout his lifetime, his collected writings not having been given to the world until 1762.

In the meantime Thierry (1), a French physician who had traveled to Spain as the medical attendant of the ambassador from his country, was permitted to read over the manuscripts of his Spanish colleague, and, on his return to France, published in 1755 the first account that appeared in print of Casal's observations.

Following this there was a considerable period during which the subject received little or no attention, and the next account we have of the malady is contained in the celebrated monograph by Frapolli, which appeared in 1771, to be followed five years later by the well-known paper of Odoardi, who looked upon the affection as a variety of scurvy.

At this point it may be of interest to observe that there is reason for the belief that pellagra had existed in Italy a number of years before the papers of Frapolli and Odoardi appeared. It is well-known that Odoardi's attention was first called to the matter by his teacher, Antonio Pujati, and it is asserted that about the same period Nascimbeni also observed the disease in the province of Venezia. It is even claimed that Antonio Terzaghi noted the appearance of this malady on the shores of Lake Maggiore about 1750.

Following the publication of the works of Frapolli and Odoardi a series of papers on the subject quickly followed: monographs appeared in 1778 (written 1775) by Zanetti, in 1779 by Alberti, in 1780, and a German translation in 1792 by Gherardini, in 1781 by Albera, in 1786-1794 by Strambio (1, 2, 3, 4), in 1787 by Jansen, in 1781-1816 by Fanzago (1, 2), in 1790 by Videmar, in 1791 by Sartago, in 1791 by Dalla Bona, in 1791 by Soler, in 1792 by Titius, and in 1792 by Cerri (1).

Of these papers unquestionably the most important are those of Strambio, who exhibited a genius for investigation and a clearness combined with an accuracy of description that has perhaps never been surpassed. Of only less value is the celebrated monograph of Gherardini, which is a classic of its kind. The papers of Albera and Odoardi are also of much importance.

With the dawn of the nineteenth century investigators seriously took up the problem respecting the causation of this remarkable disease. In 1805-1808 Buniva, by a series of inoculations in the human being, showed that pellagra is in all probability not infectious—a fact to which clinical observation has borne abundant testimony, both before and since.

Following the well-known monograph by Fanzago (written 1807 and published 1809) on the probable relationship of maize consumption to pellagra, Marzari (1) wrote his celebrated paper in 1810 in which he maintained in the most positive manner that the use of this cereal as a food is unquestionably the cause of the malady, and was

of the opinion that the result is brought about by its supposed low protein content.

In 1814 Guerreschi initiated the doctrine that just as the ergot fungus in rye produces ergotism, so closely related moulds growing in maize may conceivably set up the pellagrous process in the bodies of those who eat the cereal infected with these organisms. Although this remarkable paper scarcely deserved oblivion, its author has been entirely forgotten in the noisy discussions that have since occurred in connection with the eiology of this affection—the theory that he clearly enunciated having been later attributed to Balardini, and still more recently to Lombroso.

Some years later (1824-1828) DeRolandis repeated the experiments of his teacher, Buniva, with similar results.

In the meantime pellagra was discovered in the province of Gascony in France in 1818 by the elder Hameau, though a report of the result of his observations was not made until 1829. Notwithstanding that this observer had seen several cases in the meantime, he was by no means certain as to the true nature of the malady which he had found, and in his first paper simply referred to the disease as "an affection of the skin which is little known and which occurs in the neighborhood of the Teste." That the malady described by Hameau closely resembled the pellagra of Italy was first recognized by Dupuch-Lapointe, and quickly thereafter the identity of the two diseases was established beyond doubt by Gintrac and Bonnet.

During the two or three succeeding decades various observers reported cases of pellagra from the region where the malady was first investigated by Hameau; among these are Lalesque, Ardusset, Beyris, Arthaud, Laubarède, Costes, Burquet, Lemaire, Calès, Roussilhe, Gintrac, Marchant (1, 2, 3), and many others, the two last named having given the matter very particular attention.

It is of much interest to note that the disease was practically confined to the departments of Landes, Gironde, Haute Garonne, Auch, and the Haute and Basses Pyrenees, all of which provinces lie in the extreme southwestern corner of France, bordering on or very near the Bay of Biscay, and only a short distance from that part of Spain in which pellagra was first observed.

In 1845 Balardini (1) wrote his well-known monograph on the relationship of fermented maize to pellagra—a monograph which, while containing no new idea, served the purpose of initiating a discussion on this subject which has not ceased from that time to the present day.

In the same year that Balardini's celebrated work appeared, the great French pellagrologist, Roussel (2), published the first edition of his really wonderful treatise on the subject of pellagra, to be followed two decades later by a greatly enlarged edition of the same work. While it cannot be said that Roussel had any great experience with pellagra from personal observation, he never having lived in the regions where the affection prevailed nor practiced among the unfortunates who suffered most from this malady, his work was in-

valuable, because he was the first to systematize thoroughly our knowledge of the subject. Under such circumstances it can not be wondered at that this enthusiastic and tireless worker occasionally made mistakes that would likely not have occurred had his practical experience with the subject been greater, but on the whole his work is a monument to his painstaking care and evidently great abilities. This author early became an enthusiastic advocate of the relationship of the eating of maize to pellagra and has stated the case for this aspect of the subject with rare strength and acumen.

Following the publication of the works of Balardini and Roussel, nothing of importance was added to pellagra literature for the succeeding decade, but in 1855 a very remarkable book was published by Morelli—a book which in many particulars has never been excelled. This investigator did not, however, agree with the two eminent authors just referred to respecting the causation of pellagra, he having subscribed to the theory, commonly held by the laity and the great majority of the profession of that period, that the affection is due to a lack of good food; he, moreover, particularly insisted that the absence of aliments of an albuminous character is an etiologic factor of the first importance. In this connection the credit likewise belongs to this observer for having first distinctly enunciated the theory of monophagism—one which has recently been rediscovered, and of which much is being said at present.

In the following year appeared the almost equally remarkable book of Lussana and Frua. These writers likewise adopted the view that pellagra is the consequence of faulty and insufficient food, and, while not agreeing with the peculiar views of Guerreschi and Balardini, were in accord with Morelli in asserting that bad maize, on account of its supposed lack of nitrogenous constituents, is largely to be blamed for the production of this affection.

The succeeding decade was chiefly characterized by a discussion—at times even bitter—respecting the etiology of pellagra. During this period Bouchard (1), Landouzy (1, 2), and Billod (1) wrote books with the idea of proving that there is a peculiar form of this disease that has no association with the use of maize as a food. Simultaneously a considerable literature sprang up in opposition to the views of the authors just referred to, in which the maize theory was upheld—the principal writers taking this side of the question having been Roussel (2, 3), Balardini (1, 2), Costallat (1, 2), Lombroso (2, 3, 6, and 8), Chiotto, Lombroso and Erba, and somewhat later the celebrated Selmi. These writers held that the supposed pellagra without maize really has nothing to do with this affection, and that cases so reported were the result of mistakes in diagnosis, and were designated as "pseudo-pellagra" by Roussel. The discussion concerning the causation of pellagra initiated during this period may be said to have continued to the present day, and with such constantly increasing advantage to those who uphold the mouldy-maize theory that there has been in recent years a practically universal

acquiescence in this view by the European writers who have most studied this affection.

This period is likewise of historical interest in that changes in the central nervous system were for the first time particularly stressed by Benvenisti, though such alterations had been briefly mentioned even in the previous century by Villa, and somewhat later by Fantonetti, Brièrre de Boismont, Labus, Verga (1), and others.

The gradual advance of pellagra eastward is evidenced by the fact that Baerensprung, in 1830, and Théodori, in 1858, directed attention to the occurrence of the disease in Roumania; the latter says that Nobilis, in 1836, refers to the malady—even then called by the common names which it still bears in that country. Théodori mentions that the affection had not been at all uncommon for some 16 or 18 years prior to the publication of his paper, and had been particularly noted by his father about the year 1846.

Four years later Felix also observed the disease in the province of Wallachia, and the malady was subsequently found in all parts of Roumania where Indian corn is grown and eaten.

In the meantime pellagra appears to have been almost forgotten in the land of its birth in the old world, there having been very little written concerning it by Spanish physicians for more than a century after its discovery by Casal. It is indeed a matter of some doubt as to the extent to which the disease later prevailed in that country—an uncertainty which has persisted even to the present day. As to whether or not pellagra is now to be found in Spain is still a subject of conjecture, for we have next to no knowledge respecting the matter, at least outside of that country, and it is unquestionably true that if it still exists there to any extent at all Spanish phyisicians are strangely silent concerning it. During the period when the discussion respecting "pseudo-pellagra" was raging in France, Costellat (2) took it upon himself to make a visit to Spain, and to investigate the malady—supposed to be pellagra—which was known as "enfermedad del Higado" or "flema salada," and in a monograph describing the results of his observations declared that this disease was neither more nor less than acrodynia. Inasmuch as pellagra has disappeared from France, it is not too much to hope that it has greatly diminished or even ceased to exist in Spain, but in order that all uncertainty may be removed it is greatly to be desired that the matter be thoroughly investigated by some competent Spanish physician.

From 1860 to 1880 several Spanish works appeared, among which were those of Roel, Calmarza, Gross, and Martinez. The works of Calmarza and Roel are the most important additions to the Spanish literature on the subject that have appeared since Casal's memorable brochure; these authors' views as to the causation of pellagra are most hazy—the former appearing to regard it as the result of misery and alcohol, and the latter as an hereditary disease, the consequence of a sort of mixture of scurvy and leprosy.

This same period is remarkable for the appearance of a number of most able papers by Gemma (1-9), whose powers of correct observation have been rarely equaled. In addition to adding much to our knowledge respecting the symptomatology of pellagra, this author is notable in the history of this disease on account of his having been in his time the only opponent of the mouldy-maize theory who really made painstaking experiments in support of his views, and who relied on something more than mere assertion to prove their correctness.

In 1875 Typaldos described pellagra in the Island of Corfu, and in 1888 Major, in Hungary, and Philipowicz, in the Austrian province of Bukowina, each first called attention to its presence in the localities mentioned. More recently Aldor and Sternberg and Purjescz in 1898, Scheiber in 1899, and Veress in 1906, have made notable contributions to the literature of pellagra in Hungary.

In 1894 Rosen described the disease as being not at all uncommon in the Russian province of Bessarabia—a region inhabited by Roumanians.

In 1892 Nibbi announced that pellagra occurs in Mexico, but his paper was unfortunately so brief that it was of comparatively little value. Vales, in 1896, wrote a most excellent and complete brochure on this subject, and described the disease as it occurs in Yucatan.

Neusser (1), in 1887, called attention to the frequent occurrence of pellagra in Austria, and wrote one of the most concise, but at the same time one of the most important of all of the works that have so far appeared on this subject; his brochure is a veritable mine of accurate observations—some of which were quite new—and in addition we are indebted to him for suggestions as to the etiology that are of the greatest interest.

In 1910 Sambon announced that pellagra has nothing to do with the consumption of maize, and that it is a disease produced by a parasite transmitted by gnats (Simuleum). This is in effect a revival of the maism theory first suggested in 1780 by Jansen and later advocated in 1795 by Allioni, and in 1818 by Belotti.

As regards the history of pellagra in the United States it may be said that here, as elsewhere, our knowledge respecting the period of its appearance is more or less vague, but that it has occurred for some time to a greater or less extent in the southern part of the United States is highly probable.

So far as the records go it seems likely that the first case of undoubted pellagra originating in the United States was reported by the author (1) in April, 1902. It is true that in 1864 Gray, of New York, and Tyler, of Massachusetts, reported cases, but from the clinical records they would appear to conform much more closely to those uncertain types of the symptom-complex which the author has together called "parapellagra" rather than to those forms of the malady so commonly found in Italy and our Southern States, and that in 1883 and in September, 1902, Sherwell, of New York, published the records of cases originating in Italy, but these could have no interest of an historical or epidemiological character, since they

CHAPTER II

CAUSATION

It would probably be difficult to find any other malady the causation of which has occasioned so much speculation and which has given rise to so many different opinions as that of pellagra. This is but another way of saying that this aspect of the subject has been on the one hand to a certain extent neglected in the past by serious investigators, while on the other it has received much attention from the theorists, who have added greatly to its inherent difficulties by their speculations.

In this connection nothing could be more *apropos* than the words with which Michael Gherardini began his classical treatise on pellagra considerably over a century ago. He says:

"All things may be established theoretically. Error itself may be proved; this is an undeniable axiom, which is particularly true in medicine. The majority of physicians have ever preferred, with an appearance of belief, the effulgent chimeras of their fancy to the wise teachings of nature. Piling conclusion on conclusion, they with cunning art explore the boundless realms of theoretical medicine, and soaring to their heart's content prefer the vain glory of having advanced an hypothesis to slow and painful investigation, particularly as in the primrose pathway of theory they find no difficulties which interfere with their conclusions."

More recently Raubitschek has bewailed this tendency in the following somewhat caustic fashion:

"When we undertake the thankless task of carefully reviewing the flood of articles which has appeared on this subject, it is astounding to observe how investigation into the causation of the malady has become the playground of scientific fledglings, who, with hazy minds, want of critical ability, and no capacity for such investigation, seek as the causative agent of pellagra simple absurdities and monstrous fantasies."

Despite such opinions it should never be forgotten, however, that in Europe many able men have for nearly two hundred years devoted much time and thought to this subject, and that some of them, indeed, practically consecrated their lives to it. A careful perusal of their

writings will disclose the fact that they have built up a literature amazingly rich in facts concerning this disease, and that substantially every theory respecting its causation, put forward more recently as new, was at one period or another advocated, fully discussed and finally rejected by them. As this process of suggestion and sifting went on the patient delver into the records will plainly percieve that during the last three or four decades differences of opinion as to the etiology of pellagra exhibited an increasing tendency to disappear, and that there was a marked disposition on the part of the more prominent European investigators of this affection to agree as to its causation.

In this connection, since this monograph was primarily written for the doctors and people generally of Georgia, the author can not forbear saying a few words in his official capacity as the health officer of this State, where pellagra has raged now for many years and has caused endless suffering and countless deaths, and which bids fair to continue as a pandemic scourge for an indefinite period in the future. Moved wholly by the sufferings of his unfortunate compatriots and a desire to help them, and in no spirit of contradiction or unkindly criticism, he would call attention to certain facts which he can not but think are greatly to the detriment of all inhabitants of those regions where this fearful disease prevails.

It would seem that many of those in English-speaking countries who have taken up the study of the etiology of pellagra either wholly or in part ignore the work of European investigators on this subject; often appearing to believe that nothing of importance had been done by their predecessors in this direction, and without making any attempt to find if their ideas were new, or, if not, the objections urged against them when formerly proposed, they have in some cases assured both the professions, and, most unfortunately, also the laity, that they had discovered the cause of this affection, and have led our people to believe that they might safely disregard the teachings respecting prevention now accepted abroad as being of most value. While the author admits that it might be in certain directions of advantage to an investigator to approach this difficult question unhampered by preconceived opinions, he nevertheless feels that the subject is of such formidable complexity that a full knowledge of all established facts, especially as regards etiology, is absolutely necessary in order that a just conception of the nature of the malady may be gained, and that after which only would it be possible to formulate an adequate theory. Even after this is done our speculations should be carefully kept from the laity until they have been put to the acid-test of most careful investigation—not only by those who originate them but by other competent observers—and have been finally proved to be correct. Unfortunately in some cases none of these conditions have been observed, and, while the author would not for a moment doubt that such theories were put forward in the best of faith, it would be impossible to estimate the harm done by them should they ultimately prove to be erroneous; we can only say

that it was, is and will be very great. Attention may also be directed to the fact that the two most widely accepted of the many "new" theories recently advanced leave the poor farmer, who is the most common victim, much as they find him, since in the one case he has no way of protecting himself from being occasionally bitten by gnats, or other predatory insects, and in the other we find no sovereign balm for that poverty which it is alleged is at the basis of his afflictions. Let us therefore keep our theories, as far as possible, confined to such scientific circles as are competent to deal with them until they cease to be theories and become facts, and never forget our solemn obligation to our dependent fellow man, whose health, happiness and often even whose life is dependent on the correctness of that which we teach him.

We shall now take up the evolution of our knowledge as to the causation of pellagra, citing but briefly the opinions of the earlier writers, and showing the gradual steps by which investigators have reached their present conception of the etiology of this disease.

Views of the Earlier Writers on Etiology.

With but few exceptions the earlier writers made no attempt definitely to assign any particular etiologic factor in pellagra, contenting themselves as a rule with calling attention to those obviously debilitating influences with which the inhabitants of pellagrous districts are constantly brought in contact. As we now know that the development of the objective symptoms of this disease is closely associated with conditions of this kind, their speculations are not wholly without interest, dealing as they do with those factors which we would at the present time regard as predisposing causes.

Thus we find that the celebrated Casal, the discoverer of pellagra, seeks for the cause of the malady in the heavens, in the temper and constitution of the air, and in the diet of those so afflicted, and it is noteworthy that he opens the discussion of this phase of the subject with the statement that *maize* is the chief food of those suffering from this trouble, though, in addition, he mentions a number of vegetable substances, along with a little milk, eggs, butter and cheese. He notes that they seldom have meat. He is opposed to the view that the malady may come alone from atmospheric conditions, since all alike under such circumstances should suffer. While he rejects the idea that the malady is a simple scurvy, he finally decides that it may be regarded as a leproid form of scurvy or scorbutic leprosy (p. 352). Somewhat later he, however, remarks that the disease is *sui generis* (p. 354).

Frapolli, who next wrote on this malady, did not hesitate to assign *insolation* as the true and only cause. He, therefore, rejected the view that the malady might be contagious, hereditary, or the result of bad hygienic conditions.

Odoardi thought the disease to be a special form of scurvy, while Zanetti recognized as etiologic agencies both *bad food* and *bad water,* and in addition especially called attention to the fact that those suffering from the disease were very poor and were *eaters of maize.*

Gherardini, who was the ablest of the earlier pellagrologists with the exception of Strambio, thought the malady to be due to *bad food* and particularly *bad maize.* He discussed the possibility of animal parasites, but finally decided that there is no reason to believe that they have anything to do with the causation of the malady; he did not consider the disease contagious. Gherardini's work is remarkable for the fact that he adopted the experimental method for the purpose of settling the various questions that arose respecting pellagra, and was the first really to demonstrate that local lesions may be caused by the sun's rays.

Albera, who next wrote on the disease, agreed in the main with Frapolli, assigning *insolation* as the cause, but he likewise suggests *cereals, beans and bad vegetables,* as being etiologic factors, and particularly called attention to a supposed relationship of the malady to *rancid butter* and *oils.* He found that the malady was particularly common in dyspeptics, and first definitely advanced the view that it is *hereditary,* though this possibility had been previously suggested by Odoardi.

Videmar considered the disease as a variety of *hypochondriasis* (mal del padrone), and regarded the pellagraderms as being *impetigo;* notwithstanding, he thought it might be the result of a *miasm.*

Strambio (4), perhaps the greatest of all pellagrologists, recognized as possible factors all depressing influences, among which were *bad foods,* including *rancid oils,* and particularly *maize,* which he stated was often of poor quality. He frequently stressed a supposed relationship between pellagra and *dry localities;* he noted that *pregnancy* and *lactation* are frequently followed by a development of the disease. He was inclined to believe that the affection is *hereditary,* but was strongly of the opinion that it is not contagious. He did not hesitate to pronounce the disease *sui generis.*

Jansen agreed with Videmar as to the malady's being a variety of *hypochondriasis,* but likewise stated that it is produced by *excessive labor,* and *bad foods,* including *mouldy cereals;* he did not regard the disease as being contagious.

Soler thought the affection to be due to *inanition,* as the consequence of *misery* and *filth.*

Titus, who had no practical acquaintance with the disease, advanced the theory of its *contagiousness,* while Della Bona agreed with Casal that the affection is a mixture of *leprosy* and *scurvy.*

G. Cerri (2) regarded *inanition* as the causative agency in the production of the malady, while Allioni argued that it is caused by a *miasm* and that it is *contagious* and *hereditary;* however, it is doubtful whether his cases were genuine pellagra.

While Thouvenel proposed the extraordinary theory that pellagra might be due to the *light and cold air of the Alps meeting the humid atmosphere of the lower plains,* it is noteworthy that he was the first of the writers to urge strongly the possible connection between *pellagra* and *maize,* stating that the disease is very common in those subalpine regions where the grain does not mature, and that it is particularly frequent in those years when dearth of other cereals compelled the use of Indian corn as the exclusive nourishment.

Townsend, during his visit to Spain in 1786-87, had an opportunity to study pellagra, and took occasion in the interesting story of his travels to *argue against the leprous nature* of the malady—for as such it was at that time regarded in that country.

The next work of importance on this subject was that of Buniva, who showed that the disease is *not inoculable,* a fact which was confirmed some twenty years later by De Rolandis.

In 1807 Fanzago (2) read before the Academy of Padova a memoir in which he claimed that *maize is the cause of pellagra,* and it may be thus definitely asserted that this author was the first who unreservedly connected this cereal with the malady in question.

Notwithstanding that it was clearly the preceding writer who first categorically claimed a connection between Indian corn and pellagra, the credit is usually given to Marzari (1), whose celebrated memoir appeared in 1810.

In 1814 Guerreschi wrote a remarkable paper in which he clearly advocated the view that pellagra is caused by a *fungous growth in maize.* He called attention to the resemblance of the disease to raphania (ergotism) and showed that there is a close relationship between the ergot fungus and the moulds that are abundantly present in bad maize.

In his excellent monograph on pellagra, which was published in 1815, Fanzago (2) reiterates the belief previously expressed, and at the same time discusses in a very clear and able manner the etiologic doctrines previously proposed.

Almost simultaneously appeared the memoir of Sartogo, who cautiously refrained from advancing any opinion as to the causation of the malady in question, while Montesanto strongly argued against the view advocated by Guerreschi that pellagra and raphania are kindred diseases.

In the same year Sette (2) published his well-known paper, in which he clearly indicates his belief in the *maize etiology of pellagra,* stating that where the cereal had been replaced by potatoes the malady ceased its ravages in a short time. He does not believe it has anything in common with scurvy, and particularly notes that it *occurs in dry localities.* He saw it in people living in towns, and likewise in children two years of age.

While a number of articles of greater or less interest appeared in the interval, the next contribution of importance was the celebrated memoir of Balardini (1), in which *mouldy maize was strongly*

urged as the etiologic factor in pellagra. This year was likewise rendered notable in the annals of this disease by the publication of the first edition of Roussel's (2) masterly work—in which he fully agreed with Balardini as to the causation.

In 1855 Morelli's (2) brilliant brochure appeared, in which the view that pellagra is the result of *inanition* was strongly maintained. In this most excellent work we first find the suggestion that this disease may be the result of *monophagism.*

In the following year the classical monograph of Lussana and Frua was published; these authors also urged with great vigor and unsurpassed ability the theory of inanition—then commonly held—and unreservedly advocated the opinion that it is more especially to a *lack of nitrogenous foods* that we are to look for the determining factor in the production of this malady.

An important paper on this subject had been written in 1847 by Robolotti, though it was not fully published until 1865. This very able writer and investigator was likewise a strong adherent of the theory of *inanition.*

In 1869 the first edition of Lombroso's (2) classical treatise on this disease was published. This author at all times strenuously maintained the causal relationship of bad maize to pellagra, and wrote so much on the subject that this view of the etiology of the disease is frequently spoken of as "Lombroso's theory"; as a matter of fact this prolific writer's only contribution of importance to this phase of the subject was his advocacy of the idea that *poisons are produced in maize by the growth of microörganisms* and that these substances are the real pellagrogenic agencies. The advocates of the maize theory hold, however, that Lombroso deserves a great deal of credit for having done more than any other person to impress upon the world the supposed connection between maize and pellagra, and assert with truth that he inspired much important subsequent work on the etiology of this disease.

In 1867 Calmarza, and in 1880 Roel, each published in Spanish a monograph on pellagra, which, with the exception of the paper of Casal, remain to this day the principal works on this subject emanating from Spain. Calmarza advocated the view that pellagra is a disease produced by *misery* and *alcohol,* while Roel, following Casal, believed it to be a sort of *degenerate leprosy.*

The subsequent history of the etiology of pellagra will be found in connection with the various subdivisions into which it has been divided by increasing knowledge, and to which the reader is referred for further information.

Predisposing Causes.

Most of those who have written on this subject in the past have agreed that any and every agency that tends to lower the vitality and causes deterioration in the general health plays an important

rôle in the production of pellagra—meaning by the term those symptoms which periodically recur and which when taken together have been regarded as constituting an attack of this disease. However, as will later appear, the pathologic alterations are of such character and extent as would clearly indicate that the external and more obvious clinical manifestations are to be regarded as the common but wholly unnecessary and almost adventitious morbid phenomena which are the outward expression of these changes, and are by no means to be looked upon as in themselves constituting the disease. In this sense there can be no doubt that all influences that lower the bodily powers and decrease resistance make mightily for the production of the affection. As the symptoms thus brought about are often of the greatest severity and frequently threaten life itself, their study and prevention becomes of the greatest importance, and therefore will now be considered in detail.

It cannot be denied that all such depressing influences probably likewise play a certain part in the production of the disease itself.

It would appear to be beyond question that the *sun's rays* act most deleteriously upon pellagrins, not only developing the skin lesions, but causing an outbreak of all of the other symptoms. It seems certain that this is largely the result of the action of the *chemical rays of light*, and that it is in addition likely that the *sun's heat* unfavorably influences the delicately balanced metabolism of those suffering from this disease—just as the opposite condition of *excessive cold* may produce similar results.

It is well-known that *season* exerts a great influence on the development of the classic, more or less external, outbreaks of the affection—these occurring mainly toward the end of winter and spring, and in the autumn, *i. e.*, along about the equinoxial periods. While the *classic* form is by far more common in the *spring* months, according to Morselli the so-called *typhoid* form is most prevalent in the *fall*.

Everything that could be looked upon as being conducive to *bad hygienic conditions* is of moment in this connection, since such influences may be often traced as the determining factors in the production of an outbreak of the classic clinical phenomena of this affection. And the term "bad hygiene" has here an exceptionally wide significance. So delicate does the metabolism of the pellagrin ultimately become in some instances that an attack of the external symptoms may be brought about by the slightest disturbance or the most trifling mishap, or by some other debilitating influence of such insignificant character that it would pass unnoticed under ordinary circumstances. Among such influences none have claimed the attention of the pellagrologists more than those that are associated with the food and drink.

From Casal down to the present day writers have held that *lack of food*—both as regards quantity and quality—play an important rôle in determining the classic attacks of pellagra. A like result is

believed sometimes to follow the habit of eating *imperfectly cooked* and *indigestible* articles of diet.

Della Bona inculpated *water* as having a tendency, when bad, to bring on pellagra, and many others have shared his view, but more accurate observations in recent times by Fratini and Pagliani have seemed to dispose of this idea.

Gherardini, Cuboni (2) and many others have attributed the pellagrous attacks to a *lack of wine,* while Nobili has assumed that a similar result is brought about by its *abuse.*

Some have thought that *excessive humidity* plays a subordinate rôle in the production of the symptoms, while others have ascribed a similar result to *increased dryness of the atmosphere*—the latter so often referred to by Strambio (4, pp. 34, 42, 74, 154, 171), and urged as a causative factor by Gherardini (p. 76), Soler (pp. 30-31), Sette (7, p. 74), Calderini (2), and more than all by Marchant (1, 2, 3), who sought in the excessive aridity of the Gironde one of the principal etiologic agencies in the production of the disease.

It has likewise been thought that *changes in temperature, variations in the winds,* and *excessive atmospheric electricity* have been in some way responsible for the production of the malady.

Dark, ill-ventilated and humid habitations have likewise been inculpated by Albera, Sartogo, Soler and others, the same writers maintaining that *filthiness* in a measure also influences this result.

Excessive fatigue has been urged likewise by Zanetti, Odoardi, Albera and Strambio (4) as prejudicial to the peasant class, particularly as it is true that their activities vary greatly—they exerting themselves to the fullest during the spring, summer and autumn, and lying idle during the winter without, as a rule, proper exercise.

Benvenisti thought *excessive venery* conducive to the development of the disease.

It is thought that *sex* plays an important part in the development of pellagra, Odoardi, Sartogo, and Soler maintaining that the disease is more common in women, while Moris and Roussel (3) are convinced to the contrary. Calderini (2), who has studied this phase of the subject more carefully than anyone else, shows by statistics that the malady develops earlier in women than in men, and that it lasts considerably longer, it being therefore true that the names of the former get into statistical lists more frequently than those of the latter. It is undoubtedly true that such data as we possess on this subject, with few or no exceptions, have to do with those forms of the disease which manifest themselves by outbreaks of the classic symptoms, and fail to take into consideration the usually milder types of the so-called *pellagra sine pellagra;* such data are therefore untrustworthy. As a result of their superior strength, and as a consequence of the fact that they are not subjected to many debilitating influences inseparable from the sexual life, these less severe forms of the disease are probably more common in the male.

It is also well-known that the *puerperal state, nursing,* and *chlorosis* influence the development of the disease in women, while *fevers,*

depressing influences of all kinds, such as *excessive blood-letting* and *purgation* likewise produce similar results in both sexes. Babes (2) has especially directed attention to the fact that *syphilis* and *malaria* predispose to the disease. Sandwith (1), particularly, has insisted that *hookworm disease* is very common in pellagra, but Ceresoli (2) found in Italy that these parasites were not so often found in pellagrines as in healthy people—being 27.1% in the former and 39.4% in the latter; in 300 cases he found hookworm in 24.3%, ascaris lumbricoides in 68.3%, tricocephalus dispar in 59.3%, oxyuris vermicularis in 2.3%, and tenia saginata in 4.3%, his observations having been made in 27 communes.

Aldalli thinks that the malady is most common in women about the *menopause*.

It is a curious fact, noted by Calderini (2), that the mortuary statistics of Milan show that a greater number of male than female pellagrins died in that city.

Age is likewise of much importance.

The following tables, taken from Calderini's (2) paper, show the ages of 1,005 patients at the time of admittance to the hospital:

Men, 449—

118	were from 51	to	60	years of age.
114	were from 41	to	50	years of age.
77	were from 31	to	40	years of age.
52	were from 11	to	20	years of age.
33	were from 61	to	70	years of age.
27	were from 21	to	30	years of age.
20	were	below	11	years of age.
8	were	above	70	years of age.

Women, 556—

199	were from 31	to	40	years of age.
135	were from 21	to	30	years of age.
102	were from 41	to	50	years of age.
61	were from 11	to	20	years of age.
38	were from 51	to	60	years of age.
14	were	under	11	years of age.
5	were	above	60	to 70 years of age.
2	were	more than	70	years of age.

The following tables show the ages when the disease began:

Men, 449 Cases—

102	developed 35	to	45	years.
90	developed	before	12	years.
76	developed 20	to	35	years.
69	developed 45	to	55	years.
62	developed 55	to	70	years.
50	developed 12	to	20	years.

Women, 556 Cases—

232 developed	20	to	35 years.
137 developed		before	12 years.
79 developed	35	to	45 years.
64 developed	12	to	20 years.
35 developed	45	to	55 years.
9 developed	55	to	70 years.

The author is convinced that *dyspeptic disturbances* play a very important part in the development of pellagra. Whether these conditions are the result of the presence in the body of the pellagrogenic agency, or whether the dyspeptic condition occurs independently, there is no sort of doubt that an overwhelming proportion of pellagrins give a history of disturbances of this kind, usually for many years previous to active manifestations of the malady. It is, therefore, patients of this class who should be consistently urged by their medical advisers to avoid all the possible causes that might induce the disease, whether active or predisposing.

The author likewise has frequently observed, particularly in women, the pronounced effect exerted by *mental anguish*—a very large proportion of these patients admitting on properly directed inquiry that their first active symptoms developed closely following worry. The importance of such influences has been recognized since the time of Strambio.

It is likewise thought that *race* may somewhat influence the occurrence of pellagra, as it has been noted that certain peoples appear to enjoy a degree of immunity. Thus it was long ago pointed out by Ivaldi that the Jews in the Ghetto of the town of Acqui did not at that time suffer from pellagra, notwithstanding the fact that the poorest of them ate maize products freely. It was later shown by Procopiu that this race likewise enjoys a relative immunity in Roumania, though he asserts that Jewish pellagrins are now and then encountered in Moldavia. Still more recently Wolff has independently made similar observations in the United States.

It has long been believed that pellagra is *hereditary*. Among the earliest writers we find this idea suggested, it having been first advanced by Odoardi (p. 15), and later distinctly advocated as a theory of causation by Albera (pp. 38-39). At a still later period this opinion was fully accepted by the great pellagrologist, Gaetano Strombio (1, p. 38; 4, pp. 38-39), who said that such influences are operative in more than half of all cases of pellagra, by the Piedmont Pellagra Commission in its first report in 1845, and by Calderini (1), who finally proved the connection by extensive statistics.

However, among the older writers Soler and Facheris repudiated this view, and later Lombroso argued against the idea that the malady is directly hereditary; still more recently Procopiu has denied any such relationship.

While we find here and there an American writer of the present day who also seems inclined to dispute this view, the malady has

such a profound tendency to be transmitted from parent to offspring that it is no exaggeration to say that all European observers of practical experience have long since admitted and ceased to question the fact. The disease is too recent in this country for its hereditary tendencies to have become prominent, since it will require at least a full generation following its endemic appearance for such influences to attain their maximum development.

So well is this relationship recognized abroad that there has sprung up a considerable literature on the subject—particularly in Italy. Not only has there been a general agreement as regards typical pellagra of an hereditary character, but numerous morbid states, not always terminating in classic forms of the disease, have been ascribed to the same cause. Among these—which will be more fully described in the chapter especially devoted to the subject—are:

(1) Children who develop classic pellagra in infancy.

(2) Children born with, or developing during infancy stigmata of degeneration, as manifested in deformities and imperfect development.

(3) Children who exhibit in early life a weak constitution and poor digestion, often associated with roughness of the skin and various eruptions, and who frequently die early from marasmus.

(4) Individuals born of pellagrous parents who only show typical symptoms of this malady in adult life—such persons probably always having belonged in youth to one of the groups already considered.

By far the most complete and satisfactory statistical study that has been made on the subject of the relationship of heredity to pellagra is that of Calderini (2). This careful and accomplished investigator showed that of 1,005 pellagrins—449 men and 556 women—admitted to the city hospital of Milan from 1844 to 1846, inclusive, there were positive evidences of heredity in 618 cases, and that such influences were possible in 380 more—there being thus only 7 in whom it seemed fairly clear that no such taint existed. Of these patients 778 had passed the age of 12 before being attacked.

Inquiry developed the fact that of 6,412 persons nearly related by blood to the 1,005 pellagrins just referred to, there were 2,061 who had pellagra; this included 69 fathers and 104 mothers, still living, who had 188 brothers and 195 sisters, and 128 sons and 134 daughters similarly afflicted.

Of the 449 men 136 were the children of pellagrous fathers and 121 of pellagrous mothers, while of the 556 women, 142 were the daughters of pellagrous fathers and 178 of pellagrous mothers. These statistics show a remarkable tendency, which has been noted by others, for this curious disease to follow the line of sex in its appearance in the offspring of its victims, it being rather decidedly more common for the male to have a greater proportion of sons and the female a greater proportion of daughters who show evidences of this terrible inheritance.

The singular tendency just referred to, as well as a marked inclination toward heredity, is shown in the brothers and sisters of pellagrins; it was thus found that 449 men had 132 brothers and 131 sisters, and that 556 women had 135 brothers and 170 sisters who exhibited evidences of pellagra.

These tendencies were also shown to a pronounced degree in the offspring of the patients who formed the basis of this statistical study, nearly all of whom, as before shown, were of pellagrous ancestry. Thus we find that 449 male pellagrins had 89 sons and 76 daughters, and 556 female pellagrins had 71 daughters and 62 sons who showed evidences of this affection.

It is of much interest to note that Calderini likewise observed an extraordinarily high mortality among the relatives of pellagrins, he having found that of 10,634 individuals who were nearly connected by blood to pellagrous subjects, 3,788 were dead. Of the 1,005 pellagrins already frequently mentioned, 727 were either married or widowed, and of their 3,362 children 1,175 were dead—a mortality which would certainly suggest degenerative influences transmitted from parents to offspring of an extraordinarily severe character. This writer mentions one case where a male pellagrin had 13 children, and 12 of whom died before reaching 8 years of age.

Likewise it is stated by Calderini (2) that his assistants, Ghiotti and Longhi, determined that of 1,319 persons who were members of 184 pellagrous families, 671 were healthy and 648 were victims of this malady.

Of similar import are the statistics of Boudin, which follow (p. 40):

State of the Parents	Married Couples	Pellagrous Children Sons	Pellagrous Children Daughters
Father and mother pellagrous.....	96	116	106
Father pellagrous, mother healthy..	160	64	49
Mother pellagrous, father healthy..	175	30	38
Father and mother healthy, having several pellagrous children.....	43	59	53
Father and mother healthy, having only one pellagrous child.....	185	80	105
	659	349	391

In the foregoing is seen the curious tendency for the disease to be more often transmitted by parents to offspring of their own sex, though it would appear that proportionately this tendency is greater in the father than in the mother. These figures are unfortunately vitiated by the fact that pellagra is often latent, and consequently we could not always be sure that parents, apparently healthy, are so in reality.

This subject was also thoroughly discussed by the great pellagrologist Lussana, who in his classic monograph on pellagra and in

subsequent papers fully agrees that heredity plays a most important part in the production of the disease.

Still more recently this connection has been recognized by Roussel (2, 3), Gemma (3, 6), Seppilli and Lui, Roncoroni (1), Morpurgo, Devoto (2), Agostini (4, 5, 7), Antonini (3, 4), and others. A similar relationship has been noted in this country by several writers, and the author has likewise been particularly struck with the frequency that pellagrins give a history of the affection in members of their families—the disease, however, being much more common, it would appear, in brothers, sisters, and children than in fathers and mothers. It would likewise seem true that younger children are more commonly affected than those who were born earlier. It may be remarked at this point that this would probably be the natural tendency during the earlier stages of the gradual degeneration—particularly of the poorer classes—which the poison of this disease appears to be now producing in our people, and that it is a result in strict keeping with the author's views, presently to be discussed, on heredity in this affection.

Quite in keeping with the general law which seems to govern in such matters, about one-half of the offspring of pellagrins exhibit evidences of the presence of the malady.

From the facts cited it would seem that there could be no question as to pellagra's being hereditary, but, although the matter has been alluded to, no one appears to have made any investigations as to just how this result is brought about.

That this is not the result of infection would seem to be certain, since such an assumption is directly opposed by a multitude of facts, later to be discussed. Granting the truth of this conclusion, it would seem that the only other possible explanations are that the malady is carried from parent to offspring either as the consequence of organic change in the organs and tissues during fetal life, or through such profound perversions of metabolism as to bring about such alterations shortly following birth. Unfortunately we are not in a position at the present time to determine which of these possible explanations is correct; indeed, we are by no means certain that both do not play a part.

Since pellagrologists have touched lightly on this aspect of the pellagra question those who have given any attention to the matter have overlooked the former possibility, and have without exception assumed that the pathogenic agent acts only in such a way as permanently to weaken the tissues, and to produce a *transmitted congenital predisposition,* without causing such organic change as would be demonstrable, at least during life, by the means at present at our disposal for determining such matters. This solution of the problem was that proposed by Sacchi, who speaks of it as a pellagrous "*habitus,*" which is presumably identical with the "*fond pellagreux*" of Roussel; under the designation of *organic predisposition* it has also been discussed by Lussana and Frua, DeGiovanni and Camurri (6).

While by no means denying the possibility, or even the proba-

bility, of hereditary pellagra's being at times due to a transmitted congenital predisposition, the author is of the opinion that it is on the whole more likely that such conditions have their origin in pathologic alterations during fetal life, manifesting themselves, in constitutional weakness, in malformations of the body, and in infantile pellagra—a series of morbid states which are very common in the progeny of those afflicted with this terrible disease.

Since there might well be a disposition on the part of some to doubt the possibility of the hereditary transmission of morbid conditions resulting from intoxications, it is well to recall to mind the fact that it is generally believed that chronic alcoholism in the parent not uncommonly results in constitutional weakness and even marked degeneration in the offspring. Probably still more pronounced and unmistakable is the transmission from father to son of chronic mercurial intoxication, as shown by Kussmaul, and a number of other investigators.

In this connection it is of extreme interest to note that Gosio (7) showed that the offspring of rabbits poisoned with mould toxines are far more susceptible to the action of these substances than the young born of healthy progenitors.

Likewise of great significance are the remarkable studies of Stockard and Papanicolaou on inherited degeneracy in animals following chronic alcoholism in their ancestors. (See chapter on résumé of theories of etiology.)

Notwithstanding the author's antipathy to speculation, he can not but feel that the facts are sufficiently numerous and weighty in the present case to admit—if future investigation shows them well founded—of the suggestion that pellagra may be in all cases hereditary—a theory that will be hereinafter fully discussed. *

The maize theory in its various forms occupies such a preponderating bulk of the literature of the etiology of pellagra that the author has decided that it will be advisable to postpone its consideration until after the examination of the other hypotheses, even though

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*This view can not in a sense be regarded as new; very early the malady was looked upon by the Spanish writers as a sort of mixed leprosy and scurvy, which they believed to be hereditary, but whether always they seemed to be uncertain. Calderini (1) suggests the possibility of the malady being always inherited, but not without reservation; he says: "I am almost disposed to think that this (heredity) is almost the one and only means of its diffusion." (Sarai quasi indotto a credere che questo sia quasi l'unico ed esclusivo mezzo di sua diffusione. pp. 47-48.) In all of the foregoing there is more or less of uncertainty, without any reasonable explanation of the causes that brought about the disease in the beginning. Whether correct or not, the explanation offered by the author of the etiology of the affection not only shows how the malady may well be in all cases hereditary, but likewise accounts for its ultimate causation.

some of these have been advanced in their ancient or more modern guise within quite recent times.

We will now take up and discuss in detail the various theories that have been proposed in explanation of the causation of pellagra.

THEORIES OF CAUSATION

THEORY OF INFECTION (TITIUS, 1791; TIZZONI, 1906).

Although many of the earlier writers discussed the possibility of pellagra being due to a *contagium*, the facts were so strongly against such a conception that the view was uniformly rejected by all of the more competent investigators. It remained for the German Titius, living far away from the districts where pellagra occurred and with no practical acquaintance with the subject, strongly to urge this idea—basing the conception purely on speculation, and without being able to adduce any facts of importance to substantiate it. This action of Titius leads to the remark that pellagrologists have unfortunately been almost from the beginning plagued with the speculations of theoretical outsiders, who, with an abundant supply of hypothesis and few or no facts, have constantly managed to interfere with the labors of legitimate workers and to becloud the real issues.

On the other hand those really competent to judge opposed quite uniformly this idea; thus we find that Strambio (4), Gherardini, Fanzago (2), Marzari (1), Guerreschi, and at a later date Balardini (1), Morelli, Lussana and Frua and Gemma (6,7) utterly rejected this view. In support of the latter opinion the paper of Cipriani is of much interest, he having seen no instance of transmission from husband to wife or vice versâ in 240 cases where either one or the other suffered from this disease.

In addition to the universal belief among the best pellagrologists that there are no valid reasons for the view that pellagra is contagious, we have likewise as evidence the experiments carried out by Buniva, DeRolandis and Vigo di Bairo, who demonstrated by inoculating the blood and secretions from the lesions of pellagrins into the human being the falsity of the theory. The conclusion of these investigators are confirmed by the negative results of inoculation in monkeys, which has been so carefully carried out by Dick, and by Lavinder and Francis, of the public health service, in this country.

Notwithstanding the complete failure of clinical experience to demonstrate the contagious nature of pellagra, and in direct opposition to the results attained by the attempt to inoculate the disease in both animals and the human being, there has hardly been a time since the idea was advanced by Titius that some one has not been advocating the view that the malady is due to some special form of infection—the nature of which varies with the onward sweep of time. Thus we find Allioni, whose opinions on this subject in general are remarkable for their extraordinary lack of common sense, advanced and maintained that the affection is produced by a *contagium*, which, though never really discovered, is named and discussed as though it were a reality. About the same time we also find that Videmar, who shows in his writings a decided disposition to speculation, somewhat more than suggests that this disease is contagious—a view which is rather curious, in that he also maintains that it is really only hypochondria.

At a somewhat later period Bodei maintained that the disease is *contagious*, and is a sort of *venereal affection*. About the middle of the last century this view was also strongly advocated by Botto and Ivaldi, and somewhat later by Debreyne.

One of the most curious chapters in the history of this curious disease is the remarkable theory, hereinafter to be discussed, that was advanced by Pari in 1870, and maintained thereafter for some two or three decades with an earnestness and devotion worthy of a more reasonable cause.

With the passing of Pari the theories that assume some living poison as the causative factors in pellagra for the most part lose their highly nebulous and

impractical characteristics, and we find that more capable and scientific observers from this time onward make claims for the etiologic relationship of several microörganisms to this disease, and, ceasing irrational speculation, attempt to make their views square with the actual facts, and work out their ideas according to the latest scientific methods.

Precisely as it is now the last word in fashion to offer an animal parasite, with an intermediate host, as the causative agent in a wide diversity of pathologic processes, so was it *à la mode* to assign unhesitatingly to some low form of vegetable life a similar rôle during the last two or three decades of the past century. In that bright, heroic age of the schizomycetes a glance in the microscope was not seldom sufficient to settle the most intricate problems of etiology, and it is, therefore, no wonder that the bacteriologist early cultivated the pellagrous field, lying fallow and waiting for the plowman.

The first to enter the list was the celebrated Italian dermatologist, Majocchi, who in 1881 announced to the Royal Academy at Rome that he had found in the meal from bad maize, and also in the blood of pellagrins, an organism which he called the *Bacterium maydis*, and suggested that the germ might have an important bearing in connection with the causation of pellagra. Later this organism was investigated by Trevisan and Cuboni (1, 3 and 4). The latter observer was unable to find the germ in good maize, though always present in bad, nor could it be discovered in the blood of pellagrins. Cuboni likewise noted that this organism resisted heat far more than most other bacteria, and in obtaining pure cultures took advantage of this peculiarity; he heated the maize to a temperature of from 87° to 90° C. (188.6°-194° F.) for 10 minutes—thus killing all other germs—and then made his inoculations.

At a somewhat later time Paltauf and Heider made further observations on this organism and first recognized that it is identical with the *potato bacillus*, which had been previously described. These results were confirmed and extended by Bordoni-Uffreduzzi and Ottolenghi, who determined that in order to kill all of the germs it was necessary to sterilize mush for an hour at 120° C. (257° F.), and that all spores could be killed only by repeating this procedure. When grown on polenta (corn meal mush) the germ produces a brown pulpy mass with a fecal odor after 25 or 30 days, and when administered by the mouth to dogs causes diarrhœa; an alcoholic solution of the culture injected under the skin of the animal was followed by bloody diarrhœa, paralysis and death. Inoculation into guinea pigs, rabbits and rats of the germ alone produced no results. These observers found, like Cuboni, that this organism is constantly present in the intestines of even healthy men, and although it evidently produces toxines in polenta, it seemed out of the question that it could occasion pellagra as the result of infection.

It is interesting to note that Bareggi (1) only found the *Bacterium Maydis* in the stools of pellagrins with enteritis; he also observed this organism in the dejecta of patients who were not suffering from this disease, but who presented evidences of a chronic intestinal inflammation.

It having been thus demonstrated that the *Bacterium maydis* is in no way a specific organism, there followed a period of some years during which no investigator had the courage to announce that he had discovered the bacillus of pellagra; the bacteriologists, however, were not entirely idle, there having been made a number of interesting contributions in connection with the flora of bad maize by Monti and Tirelli, Pellizzi and Tirelli, and Tirelli (1) alone. In 1896 Carraroli (1, 3) described an organism which he named *Bacillus pellagrae*, but nothing came of it.

There then followed an unhappy period during which Ceni (2-7), generally alone but occasionally with Besta (2, 5, 6) flooded the Italian literature with a series of tedious and prolix discourses on a fancied direct relationship of the hyphomycetes to the causation of pellagra. Having observed in some experiments on chickens that when fed with either good or bad maize *Aspergilli* were common in the dejections, it occurred to these writers that the organisms might have an etiologic connection with pellagra. On further examination it was determined that the aspergilli commonly present are the *fumigatus* and *flavescens*. Still pursuing the idea of a possible direct connection of these organisms with pellagra, they examined a number of persons dead of this disease, and found that

the spores were present in their bodies in 21 out of 28 cases. They then conducted a series of experiments on chickens, guinea pigs, rabbits, apes, dogs and pigeons, and as a result convinced themselves that these organisms are highly pathogenic, not only when given by the mouth but particularly when injected into the bodies of these animals. They claim that the moulds are peculiarly virulent when introduced in connection with maize, believing that this substance exerts a marked influence over their power to produce poisons. Similar experiments were later carried out with the *Penicillium glaucum*, with, on the whole, like results. Later investigation demonstrated, according to Ceni and Besta (4), that the *Aspergillus niger* is also pathogenic. According to these writers the disease-producing power of moulds is independent altogether of their capacity to develop in the bodies of the animals into which they are injected, though Besta states that under certain circumstances there is some evidence of growth! It is significant that the writers speak of a secondary infection with intestinal bacteria when the grains of corn containing the spores of these moulds were placed in the peritoneal cavities of animals—the claim being made that the fecal organisms make their way through the intestinal walls as a consequence either of some mysterious attraction exerted by the moulds, or as a result of general lowered vitality. These writers likewise state that the spores of the *Aspergilli* have their germinative power more or less decreased by the gastro-enteric fluids of dogs, but notwithstanding this they assert that no effect is produced on their toxic power. They also affirm that the spores may remain in the tissues a long time without undergoing any alteration in vitality or reduction of pathogenic powers, and Besta (1, 2) even asserts that under certain conditions they may develop into full grown plants. It is very curious to observe that these authors quite constantly speak of the germs referred to as beyond question the pathogenic agents in the production of pellagra, and do not hesitate to characterize the lesions produced by these organisms in the lower animals as pellagrous.

In 1904 Fosatti confirmed the work of Ceni and Besta, and in addition studied the flora of fermenting maize. He concludes that the ordinary preparations of this grain used as food are not sterile, and that of the organisms which still retain vitality after cooking there is a *Streptothrix* which is capable of producing a grave enteritis when injected into the rectum, and in addition a germ very similar to the *Colon bacillus* which elaborates virulent toxines. Also these toxines have the power of augmenting the pathogenicity of the *Aspergillus fumigatus*, though they influence very slightly the disease-producing power of *Penicillium glaucum*.

In 1902, which was the same year that Ceni began his work on the moulds, Carraroli (3) investigated the *Penicillium glaucum*, and stated that he found the organism in the feces of man and beast, and in the blood, saliva, urine and cutaneous lesions of pellagrins. He asserts that the germ resists boiling even for several hours. When it is grown in the air it is not pathogenic, but when developed at from 18° to 25° C. (64.4°-77° F.), in the absence of oxygen, it becomes very virulent. When injected into man or animals it produces the characteristic cutaneous lesions of pellagra, and in the latter loss of flesh, paralysis and the anatomic lesions that occur in this disease. The writer curiously advances the view that this germ also produces spyhilis.

Palladino (2) has attacked the methods and conclusions of Ceni and Besta just referred to. He criticises the statement made by the former to the effect that *Aspergilli* elaborate in animal tissues true toxines, without it being necessary for these organisms to multiply or invade the vital organs. This Palladino justly says suggests truly a new law. We have spores elaborating poisons, which means that they absorb, nourish themselves, and eliminate. They live a latent life, renounce all their characteristics, and in order to please Ceni engage in a complex metabolism while in this condition. Ceni's critic truly says that it is necessary that a germ show powers of growth and proliferation in the system before it can be said that it infects it. Palladino likewise notes that secondary infections follow when Ceni introduced grains of maize containing the spores of moulds, while this did not occur in case he simply injected pure cultures of the organism. The explanation of this clearly is that in the former instance there were other germs introduced along with the maize seed. This writer also

strongly objects to Ceni and Besta's cocksure habit of speaking of the moulds as the infective agencies in the production of pellagra.

Experiments were likewise carried out by Antonini and Ferrati, who were unable to find any spores that were pathogenic to animals in a number of specimens of bad maize taken from pellagrous localities, nor could they discover spores of moulds in the tissues of those dead of pellagra.

In a series of experiments later carried out by Gavina (1, 2) it was found that the moulds referred to did not produce disease in animals—his results therefore directly contradicting those of Ceni.

On the other hand it is well-known that Grohe, Block, Grawitz, Baumgarten, Müller u. Retzius, Kaufmann, and Dieulafoy, Chantemesse and Widal and others have demonstrated that penicilli and aspergilli give rise to pathogenic changes in animals. It is to be noted, however, that the nodular tubercular-like lesions which they produce are entirely dissimilar to anything found in pellagra, and it is likewise true that the symptomatology is different. In speaking of aspergillosis, Renon says:

"In the bodies of both men and animals the aspergillus produces symptoms of a series of common maladies, such as acute tuberculosis, chronic tuberculosis, typhoid fever, and hemorrhagic septicaemia; while it is true that the resemblance is only partial, it is often necessary to make a bacteriological examination in order to settle the question definitely."

It is, however, the case that the characteristic and typical forms of pellagra present no sort of resemblance to any of the diseases mentioned, and we may, therefore, feel justified, both on the grounds of morbid anatomy and symptomatology, in rejecting the conclusions of Ceni and his associates. It should also be remembered that they found moulds in the bodies of pellagrins in only about three-fourths of their cases. The discovery of a common saprophyte—for such undoubtedly the moulds generally are—in the tissues of persons dying of wasting diseases, even in a majority of cases, is of no significance whatever. Bacteriologists have been all too prone in their enthusiasm to violate the postulates of Koch, one of which demands that in order for a germ to be accepted as the pathogenic agency in any disease it must be invariably found in the tissues of men or animals suffering from the malady in question.

The last and most persistent of those who would ascribe to a definite bacterium a causal relationship to pellagra is the well-known Italian pathologist and bacteriologist Tizzoni (1-6), who, alone, or in association with Fasoli, Panichi, and DeAngelis, has published numberless papers and monographs on the organism which he has described, and which he still maintains to be the pathogenic agency in this disease. The germ in question is known as the *Streptobacillus pellagrae;* two distinct varieties are recognized, which are known respectively as *A* and *B;* the former takes the form of a *streptococcus* in its growth, while the latter presents the appearance of *staphylococci.*

Type *A,* which these authors consider the fundamental form of the organism, presents the following peculiarities:

The streptococcal form of the organism shows intercalated in its chains here and there elongated individuals which present the peculiarities of typical bacilli. Occasionally the rod-shaped organisms form entire chains, or are collected in small groups. They are not regarded as degenerative forms, as they are encountered in young cultures, but the conditions which determine their development have not been determined.

The organism is discolored by the method of Gram. It passes from one branch to the other of the Carnot-Garnier tubes without changing its form. In gelatin it does not develop below 22° C. (61.6° F.). In this medium the colonies have a constant character, permitting them to be always distinguished where other germs are present; they are minute, spherical, clearly defined, exhibiting a yellowish-brown color with a tinge of marine blue, brilliantly granulated, and appear almost crystalline.

It haemolyzes blood and transforms its coloring matter into a dark blood-like substance.

In bouillon the cultures develop an acid reaction, producing coagulation in milk within 24 hours, the coagulum not being later dissolved. No development on potato. In agar the colonies are round, elevated and transparent, resembling

those of the pneumococcus without the peripheral filamentous zone which is shown on the same medium by the *Streptococcus hominis*. The organism is facultative anaerobic.

Type *B* presented the following peculiarities:

No bacilli are mixed with the cocci.

Development occurs rapidly and abundantly on gelatin at 22° C. The organism is colored by the method of Gram. It produces haemolysis to a moderate extent.

The reaction in bouillon is first amphoteric, with the production later of alkalinity.

Coagulation of milk less constant and complete, and occurs later than in Type *A*.

On potatoes it develops as a delicate coating, which is transparent and dry, and of a whitish-yellow color.

It develops abundantly on agar, with the formation of a heavy culture which is clear, afterward becoming opaque. It generally liquifies gelatin; in the beginning the colonies resemble those of Type *A*.

The organism is fixed in its microscopic and cultural peculiarities, only rarely being transformed temporarily to the Type *A*, from which it is derived. It develops best anaerobically, though it grows in the presence of oxygen better than Type *A*.

As is acknowledged by these authors, Type *A* differs but little from the *Streptococcus equi*, while Type *B* resembles a number of different staphylococci. With this organism Tizzoni and his co-workers have succeeded in producing symptoms in various animals, including the monkey, which they have interpreted as offering clear evidence that pellagra has been transmitted to these animals. Tizzoni (3) injected his germ into monkeys, and naturally detected striking symptoms of pellagra in two (genus and species undetermined), both of which died, while in two other instances the animals proved unobligingly contumacious (*Macacus sinicus* and *cercopithecus ruber*).

With the exception of Terni and Bassi none of the Italian writers seem to have regarded Tizzoni's organism at all seriously, and these investigators only write a short paper in which they say they found the streptobacillus. In the discussion which followed the reading of this paper Cesa-Bianchi remarked that Fiorani had failed to say anything of 37 cases in which he had found no germs of any kind.

Savini-Lojani has studied the blood in guinea pigs after inoculation with Tizzoni's organism, and found, as might have been expected, certain changes; there were progressive diminution in red cells, marked decrease in haemoglobin, and oscillation, though usually with an increase, in the number of white cells, conspicuous only at a short interval following the injection.

Guyot studied the lesions produced in guinea pigs by the injection of the streptobacillus, and asserts that the fundamental alteration found in the nervous system consists in disturbances of circulation, characterized by a passive hyperaemia and hemorrhagic areas. He found degenerative changes in the nerve fibers in the spinal cord, sometimes disseminated and occasionally with a tendency to become systematized, particularly in the lateral and posterior columns. Such changes might follow many acute infections, and that such a process is the result of the injection of Tizzoni's bacillus there seems no doubt, since Guyot found further inflammatory processes of a destructive character in the viscera, with hemorrhage in the intestinal tract and secondary alterations in the liver and kidneys, diffuse hemorrhages into the tissues, and profound alterations in the blood. Further than that some of the alterations in the central nervous system resemble those found in pellagra it cannot be said that the two processes are in any way comparable.

Ramella also claims to have noticed this organism in three of four cases examined.

The blood has been examined by a number of other investigators for Tizzoni's streptobacillus, and the organism has been found in the old world by those observers already mentioned, and by one American writer, Wolfe, who claims to have isolated it from a pellagrin.

On the other hand many investigators, both in Europe and America, have been unable to confirm the claims of Tizzoni; such writers as Gosio and Antonini, Gosio and Palladino, Fratini (1), Mai (1), Cesa-Bianchi and Agazzi, Babes and others in Europe, and Lavinder in this country, have entirely failed to demonstrate the presence of this organism in the bodies of pellagrins. The author has made examinations of the blood in a large number of cases, and has also sought this organism by means of cultures without ever having found it in a single instance.

It may, therefore, be concluded that aside from the inherent utter improbability of this germ (or germs) having any connection with pellagra, unbiased investigators have in an overwhelming majority of instances failed to discover it, and we may feel certain that the organism has nothing whatever to do with the disease.

This discussion cannot come to an end without mention of the valuable, extensive and apparently thorough paper by McNeal, Allison and York on the intestinal flora of pellagrins, though, on account of the inherent difficulties of the subject, no definite conclusions could be arrived at. They found that there is a marked change in the numerical relations of the different types normally found, as well as the appearance of new species; there is often a marked diminution in the number of bacterial forms present. Protozoa are frequently found. These results contradict those obtained by earlier investigators, and are opposed to what would naturally be assumed under the circumstances; it is highly probable that these results would be greatly influenced by the food.

Lastly attention should be called to the fact that there occur nowhere in the bodies of pellagrins those peculiar foci or local areas of pathologic change that are so characteristic of all infectious processes; on the other hand we find a general, systematic degeneration of all the tissues of the body, which resemble nothing so much as the changes associated with senility.

THEORY OF MIASM (JANSEN, 1788; SAMBON, 1910; RAVITCH, 1912).

As almost every conceivable opinion respecting the etiology of pellagra has been at one time or another put forward by some enterprising theorist, it occasions no surprise that the view that the malady is the consequence of a *miasm* should be advocated by speculative writers on this subject. Like practically all other views respecting the etiology of this affection, it is likewise true that this idea is old, it having been first advanced by Jansen in 1788, and subsequently advocated by Allioni and Bellotti. It was, however, nothing more than a theory, and there were at no time any facts of moment adduced by any one of the earlier writers that gave color to the suggestion. Indeed, the author should consider with Lussana and Frua that "it would be a loss of time to refute seriously this extravagance," were it not for the fact that what is in effect the same theory has been within recent years reinvented, and strenuously advocated by more than one writer—a certain appearance of truth having been lent to the view by the minute and detailed but wholly theoretical account of the method of infection given by its chief exponent.

Without any practical acquaintance with pellagra worth speaking of, and clearly ignoring the enormous amount of work that has been done on the etiology of this malady, Sambon some years ago halted long enough, in a flying trip across Italy, to inform an expectant world, even by telegraph, that he had discovered the cause of pellagra. Before leaving England he in some way succeeded in having a "pellagra commission" formed, though his writings do not make clear just how this was done. On this commission were some of the greatest names of contemporary medicine, and undoubtedly if any others of its members had taken part in the work the results would have been far different. As it was Sambon appears to have proceeded alone to Italy, whence in a few days, as before stated, he announced the discovery of the cause of pellagra, and the method by which it is transmitted. It would appear that he left his own country obsessed with the idea that pellagra is an infectious disease transmitted from man to man by some biting insect, and with admirable quickness of decision he immediately inculpated a wholly suppositious parasite and assumed that it is transmitted by one of the small gnats of the genus *Simulium*—all of which are affirmed without a shadow of proof, and in direct contradiction of the general laws which we know

usually govern the development and diffusion of those animal organisms that are transmitted by intermediate hosts. The well-known Roumanian pellagrologist, Victor Babes, of Bucharest, recently expressed himself concerning this matter as follows:

"An English commission, which had probably never before seen pellagra, on arriving in a region where the disease was common, and after seeing the pellagrins, and observing that there was a small gnat which produced a redness on the skin immediately after biting, promptly telegraphed to the world that the insect was the cause of pellagra."

The telegram just referred to, which was sent to the British Journal of Tropical Medicine on May 16, 1910, was as follows:

"The commission (Dr. Sambon) has definitely proved that maize is not the cause of pellagra; the parasitic conveyer is the *Simulium reptans.*"

As evidence of the correctness of this theory its author entered into a long discussion of the maize doctrine of the etiology of pellagra, employing the time-worn reasoning which will be duly discussed when we consider the maize theory. We will, therefore, at this point examine only the assertions of Sambon respecting the new points brought out by him in support of his gnat theory.

He has freely asserted that it was determined beyond doubt by him, during his short visit to Italy, that pellagra is a disease of damp localities, occurring along the edges of streams where gnats are most prevalent. It is rather singular that precisely the opposite has been so often asserted by the most eminent pellagrologists. While it is true that the disease has occasionally existed in damp localities, as was the case in Spain, where the malady was first discovered in the old world, it appears to have been distinctly true that the malady was far more common in dry than in wet localities. Thus we find that incomparable observer, Gaetano Strambio, frequently mentioning that this affection is one preëminently of sandy and dry places, this having been mentioned at least five times in this author's memorable monograph on this subject (pp. 34, 42, 74, 154 and 171). Gherardini likewise says that the disease is not one of the moist valleys, but is mostly found in warm and dry places (p. 76). Soler, while admitting a moist variety of the disease, brought on, he thought, by the victims living in damp places, particularly calls attention to the frequency of the disease in dry localities (pp. 30-31). Sette (1) also affirms that the affection is most common and severe in dry localities (p. 74), as has also Calderini (2). Stofella (p. 140) has affirmed that it occurs both where the atmosphere is high and dry and in localities where the opposite holds. In France Marchant (1, 2, 3) and Ardusset have particularly advocated the view that dryness of the atmosphere is closely associated with the production of the disease. The author has visited a great many pellagrins in their homes, and has never been struck with any connection between the nearness of streams and the frequency of the affection; on the other hand, inasmuch as our agricultural classes, fearing the neighborhood of streams and lakes on account of malaria, wherever possible construct their habitations at a distance from them, the great bulk of our pellagrins, therefore, live in dry places.

It has likewise been shown by Babes (3, 5), Faggioli, and Fiorani and Bassi that pellagra occurs in districts where the simulium is entirely absent, and that there are still other places where this gnat is common without the existence of this malady. Terni, Benzi, Fiorani and Bassi have recently shown that in the province of Lombardy there is no special species of gnat which habitually attacks man, with a *habitat* restricted to the same locality; that gnats exist in abundance where pellagra is absent; and that in more than 500 persons, not pellagrous, who were occasionally bitten by gnats, there was not the slightest indication that the disease had been transmitted to them.

We thus see that there is no foundation in our best literature for Sambon's attempt to support his theory by asserting that the disease is most common in those places where gnats most frequently occur.

In his attempt to substantiate the gnat theory of transmission Sambon made several assertions that have since been disproved. Not being able to demonstrate his wholly theoretical parasite, he constructed an equally suppositious blood picture which was to be characteristic of this peculiar infection. This matter has, however, been fortunately thoroughly investigated in

recent years by very competent observers, who have not only failed to find any parasite in the blood, but have simultaneously been unable to determine that there is any characteristic blood change in this disease. Maj (1) has given particular consideration to this matter.

Another assertion of Sambon has been found to be wholly gratuitous, namely, that pellagra is common among infants. It has been clearly shown in reports by the Italian Pellagra Commission (1, 2) that this disease is exceedingly rare in children during the first year of life; of the 34 provinces where pellagra occurs this commission investigated 22, and in none were nursing infants found with this disease, notwithstanding that 16,844 children were examined where the records were kept, and a large number in addition who were not counted.

Carletti (3) has recently shown that the theory is opposed to too many well-recognized facts concerning pellagra to be tenable.

Related to the theory of Sambon is that of Ravitch-Eisenman-Purdy, which, though somewhat vague, appears to assume that horses die in Kentucky of a disease somewhat similar in symptomatology to those equine affections known to be caused by trypanosomes; in this district many migratory birds, particularly blackbirds, spend a portion of the year, and are assumed during the winter months to visit the districts infected by pellagra. These writers then appear to conceive that the trypanosomes are transmitted by some biting insect from the horse to the blackbird, that the latter then flies away to a distant rendezvous, where he meets a mosquito, who sucks in the blood parasite, and then maliciously carries it off and gives it to the human being! There would appear to be some doubt about this method of transmission of pellagra.

In concluding this phase of the subject, attention should be directed to the fact that Sambon and Ravitch ignore a very well understood law respecting the transmission of disease-producing agencies by intermediate hosts. It appears to be generally true that for a biting insect to acquire the power of transmitting parasites it must live in very close relationship with the animal which it stings, and to which it incidentally communicates such infections. As the parasites conveyed in this way are, so far as known, always of animal character, and as they are exceedingly delicate and exact respecting the conditions under which they may exist, it seems to be nearly always the case—though there are some exceptions—that they only survive in the body fluids of the one intermediate and the one definitive host. As concrete examples of this general tendency may be mentioned the different forms of bird malaria; these are conveyed by the common culex mosquito, and it is a well established fact that these insects can not convey the infection to man. The anopheles mosquito, on the other hand—particularly those species that convey malaria—are preëminently domestic, and live very largely in human habitations. For the foregoing reasons then it seems improbable, *a priori*, that gnats which live in the open, and have no ordinary association with the human being could convey to him a disease which, so far as known, only occurs in man.

Finally we should remember that not only have we found no parasite in the bodies of pellagrins, but that at least three careful and enthusiastic observers have failed to reproduce this disease in the human being by inoculation, and that similar experiments on monkeys and other animals have likewise proved fruitless. Furthermore the lesions in the bodies of pellagrins are not those of an infection, but are highly characteristic of chronic intoxications.

THE AMOEBIC THEORY (LONG, 1910).

Long found amoebae in the stools of 50 persons out of 52 suffering from pellagra. He suggests that the malady is the consequence of an injury to the intestinal mucosa by these organisms, resulting in an inflammatory process extending throughout the alimentary tract, with a consequent interference in the absorptive powers of the intestine, and a decrease in the normal ferments produced by the glandular tubules of the tract. Later, owing to the long continued inflammation in the intestines, the pancreas and liver undergo inflammatory changes which interfere with the quality and quantity of the digestive juices, with a resultant faulty digestion.

This theory is totally lacking in probability. It is well-known that persons with intestinal disturbances of all kinds, such as are common in pellagra, frequently pass amoebae with their stools; indeed, such organisms are common in normal individuals, as it has been shown that they may be demonstrated in the feces of many healthy people after the administration of purgatives, and therefore their mere presence is not of sufficient importance to create alarm—they being under such circumstances merely harmless saprophytes. If there were any truth in this theory we should certainly expect pellagrous symptoms in amoebic dysentery, while it would appear that such manifestations are excessively rare in the unfortunate victims of this malady, notwithstanding that it is accompanied by an inflammatory condition of the intestinal tract incomparably more severe than is ever seen in pellagra. The author has notes of about 70 cases of amoebic dysentery, the disease having existed all the way from a few weeks to 10 or 15 years, and never in a single case were there any of the common symptoms of pellagra, exclusive of the diarrhoea. The late Reginald Fitz, of Boston, in a private communication to the author about the year 1900, informed him that he had under his care a case of amoebic dysentery, the malady having been contracted in the South during the War Between the States, and that notwithstanding the long continuance of the disease the patient was still in an excellent general condition. If amoebae produced pellagra, cases of this kind should certainly show symptoms of the malady. It is further true that none of the clinical phenomena ordinarily encountered in pellagra were up to a few years ago described in any of the literature on amoebic dysentery—save only the diarrhoea.

Nor is it true that we find the pathological changes in pellagra which this theory would necessitate; the intestinal tract in the great majority of instances in this disease shows little ulceration, or change of any kind outside of atrophy of its muscular walls, nor do we find pronounced inflammatory changes in the digestive glands of the abdomen.

FILARIAL THEORY (ALLESSANDRINI, 1911).

Some years ago Allessandrini wrote several articles in which, without a shadow of proof, he claimed that pellagra is the result of drinking foul water in which are present the larvae of filaria. It is amusing to note that he takes strong exception to the theory of Sambon, and asserts that the epidemiological data do not agree with this hypothesis.

It is very interesting to observe that a similar possibility had been discussed by Gherardini over a hundred years ago, who, with his usual good sense, rejected it; this great pellagrologist also rejected the idea that pellagra might be due to other animal parasites.

Fratini (2) has recently shown that pellagra occurs quite irrespective of the character of the water drunk in many Italian provinces.

COLLOIDAL ALUMINUM SALTS THEORY (ALLESSANDRINI AND SCALA, 1913).

After maintaining the theory just referred to for a short time, Allessandrini suddenly discovered that his previous notions were entirely wrong, and he now, with Scala, asserts quite as firmly, and with just as much reason, that the only true and real cause of pellagra is the presence in bad water of colloidal salts of aluminum. A discussion of this view is wholly unnecessary.

ATMOSPHERIC THEORY (THOUVENEL, 1798).

Although many of the earlier writers suggested that the state of the atmosphere played an important part in determining the development of pellagra, it remained for the French writer, Thouvenel, to propose the curious and bizarre theory that the disease is the result of the light and cold air of the Alps meeting the humid atmosphere of the lower altitudes and producing a state of the atmosphere which causes the disease.

ELECTRICAL THEORY (VAY, 1832).

Another theory quite as fanciful was that of Vay, who imagined that electricity accumulates in the skin of the patients in the spring, and in some unexplained way occasions the development of the malady.

WATER OF VEGETATION THEORY (ROZIER).

Early in the last century a prominent French agriculturalist, the Abbé Rozier, suggested that what he called the "vegetable water" must be removed from all grains in order that they may be wholesome. He was evidently an acute observer, and while he had no very clear conception as to how the effect was produced, there is no question but that he was right in his conclusion. Certainly the water left in cereals has much to do with their becoming mouldy.

Inasmuch as the edible products of maize seem to be nowhere in the world properly cooked before being consumed, it is rather singular that no one has as yet suggested the habitual eating of uncooked starch as a cause of pellagra.

MAIZE THEORIES.

Not only have we had a wide diversity of opinion respecting the different supposed pathogenic agencies that have been thought to produce pellagra, but there has been even among those who regard maize as the causative factor much speculation as to the exact manner in which the cereal brings about this result. Thus we find that the maize theory of the etiology of this affection may be subdivided into a number of lesser theories, all of which present points of interest of both a theoretical and practical character.

It is to be noted that not all of the theories included in the following list have a necessary connection with Indian corn; monophagism, the eating of unleavened bread, an aliment lacking the necessary nutritive principles, the presence in the food of photodynamic substances, and the absence or decrease in vitamines might equally apply where any other cereal formed the basis of the everyday dietary of a community. Notwithstanding this, it is a fact that wherever endemic pellagra prevails, maize either forms the basis of the food of the common people, or, at the least, is very largely eaten, and it therefore follows that for practical purposes these theories may be intelligently discussed only in connection with the common use of this cereal as an aliment.

Historically these theories may be classified as follows:

(1) Insufficiency of maize as food (Fanzago, 1807; Marzari, 1810).

(2) Fungous growths (moulds) in maize (Guerreschi, 1814; Balardini, 1845).

(3) Monophagism (Morelli, 1855).

(4) Maize smut *(Urido Maydis)* theory (Pari, 1870).

(5) Toxic ferments of maize (Selmi, 1876-77; Romaro, 1908; Camurri, 1910).

(6) Unleavened bread theory (Faye, 1880).

(7) Autointoxication theory (Neusser, 1887; DeGiaxa, 1903).

(8) Mixed good and mouldy maize theory (Gherardi, 1905).

(9) Photodynamic theory (Aschoff, 1908; Horbaczewski, 1910).

(10) Vitamine theory (Funk, 1914).

Of the foregoing theories only the first two have gained any considerable number of adherents, and one or the other was generally meant in the past when the "maize theory" was referred to.

It is now in order to discuss in detail the various theories to which reference has been made, but for the sake of convenience it is not considered advisable to examine them in historical order.

Before, however, considering in detail the arguments which have been adduced for the purpose of showing the relationship between the consumption of maize products and pellagra, a few remarks on the history of this cereal may not be without a certain interest.

History of Maize.

The earlier history of maize is enshrouded in the mists of forgotten ages, no one at the present day being able to determine definitely the country of its origin. True, it is generally assumed that this plant originated in America, as its common name "Indian corn" would indicate, but even this is a matter of dispute. Rifaud is said to have found the seed of the plant in the sarcophagus of a mummy discovered in Thebes. It is likewise asserted that it is perfectly described in the Chinese work, "Li-Chi-Tchin," which was written about the middle of the sixteenth century. Its home is placed by some in Anatolia, and by others in Arabia the Happy. However, it is exceedingly probable that these differences have largely arisen as a consequence of confusion in names. At any rate, if the plant had been known in the East before the discovery of America it could only have been regarded as a sort of vegetable curiosity, and could not have formed the staple food of those countries, as under such circumstances frequent and general reference to it in all works of that period would certainly have occurred. Humboldt expresses the opinion that there is no question of maize having been originally an American plant, and that it was given by the new world to the old. It may be regarded as certain that this cereal was imported from America to Europe shortly after the discovery of the former by Christopher Columbus. Naturally it was first carried to Spain; the exact time, however, at which this occurred is a matter of doubt, though its cultivation could not have attained to any great importance before the seventeenth century. Gaspard Bauhin says, in his celebrated work *Theatrum Botanicum*, which was published in 1668, that up to that time wheat was the principal aliment of the people of Europe, Asia and Africa.

However uncertain we may be as to the period when maize became a common food in Spain, it is known with considerable certainty at what time it first came into general use in Italy. Zanon, who has made most minute investigations into the matter, finds from the old Venetian archives that it was after 1620 that the grain became in that province an article of commerce.

According to Facheris maize was first imported into Bergamo in 1652, and later cultivated in some parts of this province.

According to Lussana (3) maize was first planted in Italy by Benedetto Miari, of Belluno. This information was obtained from a book on agriculture written by Barpo in 1634. In 1640, in another book published by the same author, the statement was made that "agriculture was miraculously augmented twenty years before by the introduction of Indian corn." It would thus appear that maize was first introduced into Italy somewhere about 1620.

The first accurate account which we possess of these plants actually growing in Italy is from a monograph on the pest, which was written by Radici, of Gandino, who says:

"In the year 1632 the first field of maize (melgotto) was planted on the hillside called La Costa, below Corno, in the county of Clusvene, and everybody went to see the sowing of this new grain, which had never before been seen in Italy, and was brought into the country by a forester."

It has been shown by Marzari, Sette and others, that it was but little used in Italy up to the last decade of the seventeenth century. Indeed, Italian records clearly indicate that maize did not become a common food and was not sold in the markets until the earlier years of the eighteenth century, and in some places it was even considerably later before it came into general use. It is in the highest degree probable that it did not become a staple food of the inhabitants of northern Italy until 50 or 75 years prior to the discovery of pellagra.

In France the cereal was known during the reign of Henry II, but it was not until the second half of the eighteenth century that the grain was planted in sufficient quantity to be seriously considered as a food. Roussel (2), from whose well-known book the foregoing facts were largely obtained, traces in detail the history of the introduction of maize into the various French provinces, and in concluding this part of his work says:

"On analyzing the short history of the cultivation of maize in France and comparing it with what we known of the history of pellagra in the kingdom do we not find an exact correlation, indeed, I might say an invariable connection, not alone between the epoch when the American cereal became the popular food and that during which pellagra developed, but in addition between the quantity of maize which is consumed in a country and the degree of the development of the malady and the number of its victims?" (p. 358.)

In this connection it is extremely interesting to observe that the period at which pellagra made its appearance in France not only closely corresponded to the time at which maize was introduced as a food for the human beings in that country, but that this disease decreased in a strict correspondence with the gradual diminution in the quantity of the cereal used for this purpose, until at the present day it is generally agreed that pellagra does not exist, and

we have it on the best authority that Indian corn is no longer employed as a substitute for more wholsome starchy substances. *

Sergiu says that maize was introduced into the danube provinces by Serban Cantacuzene I, about the middle of the seventeenth century, but Roussel says this is an error, and that Prince Nicolas Maurocordato first brought the cereal into these parts in 1710.

Chemical Composition of Maize.

It is a well-known fact that the chemical composition of maize varies to a considerable extent. Not only do the constituents of this cereal vary in different countries, but there is a considerable difference in its component parts, depending on the altitude, temperature and soil where it is grown. It is likewise the case that these factors are influenced to a considerable extent by the different varieties of the grain, the proportion of proteid material exhibiting marked variation even when grown under identical conditions. While this subject is one of much interest, and should bear strongly on the question of the probable connection of maize to pellagra, the limits of this volume do not permit of anything like an extensive discussion of the matter, and those therefore who may feel an especial interest in this phase of the subject are referred to the many excellent books on Indian corn. For the purpose of this volume it would seem quite sufficient here to consider only the average composition of this cereal in the United States.

The following tables, taken from an article by Woods, published by the United States Department of Agriculture, furnish such data as would seem necessary to an intelligent discussion of the matter in this connection; the figures from the first table were obtained from the New Jersey Agricultural Experiment Station, while those of the latter represent the average of many analyses made of American cereals as found in the open market:

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*Not being able to learn from medical sources the exact extent to which maize is used as a food in France, the author some months ago addressed a communication to His Excellency, Jules Jusserand, French Ambassador to the United States, begging him to be good enough to furnish information on this point; he replies as follows:

"I have no possibility, to my great regret, to give you the exact amount of maize that serves for human consumption in France.

"The statistics at my disposal simply show that the production of this cereal is on an average of about six million quintals a year. But I can tell you, as being an absolute fact, that an extremely small proportion of that amount is used for human food, almost the whole of it being employed for cattle."

TABLE 1.—*Composition of Different Portions of a Grain of Corn (Maize).*

Portion of Corn Kernal.	Proportion in Original Grain.	Water.	In Water-Free Material. Protein.	Fat.	Total Carbohydrates. Starch, Sugar, Etc.	Crude Fiber.	Mineral Matters.
	Per Cent.	Per Cent.	Per Cent.	Per Cent.	Per Cent.	Per Cent.	Per Cent.
Whole kernel	100.0	24.7	12.7	4.3	79.3	2.0	1.7
Skin	5.6	15.3	6.6	1.6	74.1	16.4	1.3
Germ	10.2	29.6	21.7	29.6	44.7	2.9	1.1
Endosperm	84.2	24.7	12.2	1.5	85.0	.6	.7

TABLE 2.—*Average Composition of Cereal Grains.*

Kind of Cereal.	Water	Protein.	Fat.	Total Carbohydrates. Starch, Sugar, Etc.	Crude Fiber.	Mineral Matters.	Fuel Value Per lb.
	Per Cent.	Per Cent.	Per Cent.	Per Cent.	Per Cent.	Per Cent.	Calories
Indian corn	10.8	10.0	4.3	71.7	1.7	1.5	1,800
Barley	10.9	11.0	2.3	69.5	3.8	2.5	1,735
Buckwheat	12.6	10.0	2.2	64.5	8.7	2.0	1,600
Kafir corn	12.5	10.9	2.9	70.5	1.9	1.3	1,630
Oats	11.0	11.8	5.0	59.7	9.5	3.0	1,720
Rice	12.0	8.0	2.0	76.0	1.0	1.0	1,720
Rye	10.5	12.2	1.5	71.8	2.1	1.9	1,740
Wheat	10.6	12.2	1.7	71.3	2.4	1.8	1,750

Woods says:

"As far as these figures show, the average water content of these cereals is almost the same, ranging from 10% to 12%. Corn (maize) on an average contains 10% protein, which is about 2% less than the average rye or wheat contents, but 2% more than the average rice. Its fat amounts to 4.3%, or about the same proportion as is found in oats, and over twice as much as in most of the other grains In the proportion of starch they contain, corn, wheat, and rye, are practically the same, and surpass all the other common grains except rice. The cellulose content of corn is smaller than that of any of the other cereals except rice, and it also contains a comparatively small proportion of mineral matters."

From the foregoing a fairly accurate idea of the chemical composition of American maize may be obtained, though it should be mentioned that its various component parts vary not inconsiderably, as is shown by the very complete and far more exhaustive tables of Dietrich and König (pp. 520-538).

While in a general way the main constituents of maize have long been known, up to a comparatively short time ago there existed little accurate knowledge as to the true chemical composition of this cereal. Several of the earlier writers, who regarded pellagra as a disease of inanition, strongly urged that Indian corn is not sufficiently rich in nitrogen to be an ideal food, but no one appears to have made an accurate study of the subject until the matter was taken up by the American chemists, Chittenden and Osborn, who published a most interesting paper on this subject in 1892. These writers state that really nothing of importance had been done in this connection previous to their own studies, with the exception only that Rittshausen, in 1872, referred to a body discovered by him in maize which was soluable in alcohol and called "maize fibrin," and that Weyl makes the bare statement that the seeds of this plant contain a globulin-like substance soluble in 10% salt solution, and which after purification coagulates at 75° C. Long previous to this, however, Gorham had isolated the first named substance.

Chittenden and Osborne after an extended investigation were able to determine that maize contains several distinct proteids of characteristic composition and reactions. Of these there are three *globulins,* one or more *albumins,* and an *alcohol-soluble protein.* The proteids obtained by extraction in 10% salt solution were found to be a mixture of two or more globulins differing from each other in composition, coagulation points and chemical behavior; one of them is a myosin- and the other a vitellin-like body. The third globulin is characterized by extreme solubility in very dilute solutions of phosphates and sulphates. An aqueous extract of maize meal, as well as a sodium chloride extract, contains, in addition to the globulins apparently likewise *two albumin-like* bodies, more or less coagulable by heat, and differing from each other in chemical composition. Particularly noteworthy is the presence in the maize kernel of the substance known as *maize fibrin,* or better as *zein,*

which is soluble in dilute alcohol, but insoluble in water. Zein is characterized by its resistance to the action of dilute alkalies, by high carbon content, and by the ease with which it is converted into an insoluble modification on being warmed with water or very weak alcohol. Soluble zein and the insoluble modification have the same chemical composition.

In a paper published by Osborne some years later the investigations just referred to were further extended. The writer concludes that there are no true albumins in the maize kernel, but finds three globulins soluble in saline solutions, the first being called *maysin,* the second *maize globulin,* and the third *maize edestin.* In addition there is also *zein,* which on digestion with pepsin and hydrochloric acid is converted into proteoses and peptones. The writer also finds some proteid matter which is insoluble in water, salt solutions and alcohol, but is dissolved by dilute alkalies and acids.

Somewhat later Kossel and Kutscher demonstrated in zein *arginin* and *istidin,* and Millon and Molisch showed that it contains *tyrosin* and a group of *hydrocarbons.* The more intimate chemical composition of zein has been very thoroughly studied by Langstein, this writer making his investigation by the well-known method of hydrolysis of Fisher. In this way he was able to isolate *Alanin, leucin, asparaginic acid, glutaminic acid, phenylalanin, pyrolidin-carbolic acid,* and a sustance which is probably *amino-veleranic acid.* This author likewise showed the zein contains a relatively large amount of *glutaminic acid,* and especially *phenylalanin*—there being no other protein in which a larger amount of the latter substance is found. Langstein concludes, as a result of his studies, and of those of the other investigators mentioned that the protein mollicule of this vegetable is no more complex than animal albumins.

In Abderhalden's well-known text-book on physiological chemistry this writer states that 100 grams of desiccated zein contains 7% of *phenylalanin* and 10% of *tyrosin;* other albumins only show from 1.2% to 4.4% of the former and from 1.1% to 5.2% of the latter. The much discussed ferric chloride reaction employed by Gosio as a test for maize decomposition would appear to have a relationship to the extraordinary amount of the former substance as it is well-known it is a phenol derivative.

Inasmuch as about half of the protein matter of Indian corn is made up of *zein,* its intimate chemical composition has recently assumed great importance as a consequence of Abderhalden's discovery that many of the amino-acids that go to make up proteins are individually of the highest significance in connection with nitrogenous metabolism. Of particular importance seems the fact that zein contains no *tryptophane* and no *lysine*—the former being necessary for the maintenance of a protein balance in the economy, and the latter being essential for development. Experimental truth of this relationship has been particularly shown by Willcock and Hopkins, who demonstrated that the addition of *tryptophane* greatly

improved the nutritive power of a dietary in which zein was the sole albuminous substance present. The addition of *tyrosine* produced no appreciable improvement in this diet. It was observed that while this diet was being employed the animals died much more quickly if subjected to a constant comparatively low temperature.

It was likewise shown by Henriques that the nitrogenous balance could not be maintained by feeding *zein* alone, though that it has certain nourishing properties was shown by the fact that the nitrogenous loss was much less in animals fed on a diet in which this substance was the sole proteid than in cases where no albumin was given at all.

Of similar import are the results obtained by Wheeler, who showed that neither *gelatine* nor *zein* can replace more than half of the protein in any food given to mice.

A number of most interesting papers have been written on this subject by Osborne and Mendel (1), who have particularly shown that *tryptophane* is indispensable for maintenance of nitrogenous equilibrium, and that *lysine* is necessary for the growth of young animals; unfortunately neither of these amino-acids are present in zein. However, a food made up of *zein,* to which appropriate quantities of *lysine* and *tryptophane* were added, did not, when fed to animals, produce that rapid and prolonged growth that might have been expected. It therefore seems that some other undetermined factors are of importance. Other experiments by these writers would seem to indicate the desirability of increasing the proportion of *arginine*—which, like *histidine*, is almost lacking in zein—by artificially adding it when zein is being used as a food. In another paper Osborne and Mendel (2) show that the absence of *glycocoll* in zein is of no particular importance; this fact is indicated by its absence in many albumins that are known to be perfect foods, such as *casein.* The great importance of tryptophane was made clear by proving that the addition of 3% of this substance to zein at once checked the general failure in bodily functions and loss of weight in the animals upon which the experiments were being made.

One of the most interesting of recent papers on this subject is one by Rondoni (2). This writer carried out experiments the results of which were in entire accord with those just referred to. He suggests that the vitamines, or at least the alcohol-soluble correctives of maize, are not contained in the husk of the seed of this cereal, and that the whole seed is uniformly poor in vitamines; there is, he thinks, a considerable variation in these particulars in different varieties of this cereal; it is likewise not improbable that secondary modifications of the chemical composition of Indian corn depend on its degree of ripeness when harvested, the manner of its conservation, and to possible loss in constituents from various causes. He demonstrated that profound histologic changes occurred in the bodies of animals poisoned by eating sound maize, though in no instance could these alterations be looked upon as strictly corresponding to those that occur in pellagra; of particular interest

were the lesions noted by him in the thyroid and other ductless glands. He discovered the important fact that adrenalin possessed the power of correcting the bad effects of a maize diet; this fact is in close association with his demonstration that the adrenals of animals fed on maize contained much less of the active principle of the gland than was found in normal animals. The alcohol-soluble substances present in cabbage is likewise beneficial to animals poisoned by eating maize.

Digestibility and Assimilability.

The digestibility and nourishing power of maize products have been questioned almost from the time the cereal became known to Europeans. Thus we find from the earlier Spanish writers that those subsisting on Indian corn were weak and in many instances showed even obvious external signs of disease. DeSolis speaks of a cutaneous malady among the Mexicans called "ressori," which is probably identical with our pellagra. Bauhino, Tissot, Hernandes, Joseph Frank (2), and others of a like opinion, and almost all of the early writers on pellagra mention that the usual diet of the unfortunate victims of this malady consists largely of maize, and that this cereal is indigestible: Soler especially insists on this fact. More recently this view has been fully sustained by scientific investigation.

Although as early as 1879 Rubner showed that the albumins of maize are not digestible, the first writer who appears to have made accurate investigation on this subject was Malfatti, who as early as 1884 determined that in the human being 7.3 to 31.5 of the total nitrogen content in meal made from Indian corn is lost during the process of digestion—the amount wasted depending upon the way in which the product is cooked.

Some years later Neusser (2) attempted to account for the production of pellagra by assuming that maize is not assimilable, and that it contains a mother substance which when improperly digested acts as a poison.

Some years later DeGiaxa (2), in a most interesting and well thought out article, arrives at a somewhat similar conclusion. This investigator made analyses of 27 samples of meal personally obtained from pellagrous families, and compares them with the average chemical composition given by König in his well-known work. By analyzing these results it was found that the meal obtained from pellagrous families shows a greater percentage of humidity and a less amount of proteids than is normal.

DeGiaxa (1) refers to the fact that maize as it is eaten in Italy is badly prepared and improperly cooked, it being almost universally consumed as "polenta," which dish is prepared in the following manner:

The meal is sifted and placed in a copper pan, and then there is added almost double as much boiling water as meal; the mixture is placed on the fire and continually stirred—it being regarded as

sufficiently cooked when the mush easily detaches itself from the spoon used in stirring; the duration of cooking is usually about twenty minutes. On account of the evaporation of water which is very rapid during the process, the temperature of the porridge does not rise to the boiling point, and at the end of cooking is only a little above 80° C. (176° F.). It is noteworthy that further chemical analyses showed that the quantity of fats is considerably reduced during cooking, there being when the process is ended not more than half the usual quantity of such substances. That writer showed by analyses that although polenta is usually cooked in copper vessels, there are no traces of salts of this metal in the finished product.

It is, of course, clear that the Italian polenta is nothing more nor less than the American mush, though the method of preparing the two is somewhat different. In some parts of Italy maize is likewise sometimes used in the preparation of a form of bread that is called in that country "pan giallo."

In this connection reference should be made to the fact that in the southern part of the United States, where maize products are almost universally used, the method of preparation is as a whole somewhat better than that just referred to. The great majority of our maize-eating population consume this cereal as *cornbread* or *hoecake,* the two differing only in that the latter is usually somewhat thinner and is cooked in an uncovered vessel. The preparation of the dough for this bread is simplicity itself. The meal is sifted into a vessel, salt added to taste, and a sufficient amount of water to give the mixture a proper consistency. It is then placed on the fire and cooked rapidly. Generally speaking, the crust is sufficiently cooked, but there is always a soft interior where this process is practically never complete—this part of the "pone" being often of almost the consistency and appearance of the original dough. Maize is likewise eaten by the better classes in the form of "batter-bread," in which case it is mixed with wheaten flour, but again in this instance is never properly cooked.

DeGiaxa (1) made a number of investigations to determine the digestibility of the nitrogenous portions of maize when eaten as polenta. He found that in three persons to whom 108 grams of maize albumins were administered that 27.4% of this substance was passed in the feces; that writer not only regards this high loss of nitrogenous material as being detrimental as a consequence of the loss in food value, but he calls attention to the fact—and this certainly cannot be gainsaid—that the presence of such quantities of undigested albumin in the intestine must necessarily give rise to the growth of multitudes of microörganisms, with the probable formations of poisons which not unlikely result in bringing about autointoxication and perhaps more or less catarrhal trouble in the intestinal mucosa. This writer's conclusions are certainly interesting, and doubtless of importance, particularly when we remember that it has been shown that the *Colon bacillus* acquires the power of producing particularly virulent toxines in the presence of maize products.

These conclusions are entirely in keeping with those of Szumowski. This observer fed zein mixed with sugar to dogs and found that even after five hours 85% of the former substance was still undigested in the stomach and intestines of the animals experimented upon. He also dissolved this substance in 1% solutions of soda (sodium hydroxide) in water and introduced it into the animals' stomachs, and noted that this was invariably followed by marked disturbances. When the zein was injected directly into the circulation of dogs poisoning resulted; the protein was fixed by the liver; this procedure was followed by no evidence of immunity. Szumowski also fed maize to guinea pigs, and found when they were exclusively nourished on this grain that they rapidly deteriorated and died—about a month being as long as any of them lived. When he added zein to the food the animals died in from 24 to 48 hours, whether the food administered was made from maize or other grains. The symptoms observed resembled those of phenol poisoning.

Scheunert and Grimmer have made similar experiments on horses, and have come to the conclusion that maize passes through the intestinal tract more rapidly than oats, and on account of the great amount of carbohydrates the reaction of the feces becomes acid as the result of the formation of lactic acid, and that quantities of gases are produced.

Baglioni next made some interesting contributions to this subject; he placed together in test-tubes zein along with commercial pepsin, and infusions of the pancreas and of the intestinal mucosa of dogs and pigs, and then set the mixture aside in a thermostat at 37° C. (98.6° F.). While partial digestion of the albumin occurred, this in no instance was entirely completed, even though the observations were carried on for as much as a month. The investigator thought that perhaps this might be partially the result of the ferments being weakened by the products of digestion.

Baglioni concludes that maize alimentation long continued results in an increasing toxaemia, which is largely the result of zein.

Baglioni also showed that zein is more refractory to the ferments of the pancreas than to pepsin, and that the *succus entericus* of the dog has an exceedingly slight affect on this albumin.

In this connection attention should be especially called to the fact that Rubner particularly has insisted on the varying biologic value of different proteins. According to this author the minimum of animal albumin necessary for an average individual is 36.27 grams in 24 hours; the amount, however, must be considerably increased where vegetable proteins are eaten—the minimum requirement where potato alubumin is used being 38.7 grams, and where cereals are employed 84 grams in a day and night. This author asserts that 19% of the albumins of maize are lost during the process of digestion.

More recently Thomas has constructed a physiologic scale for the purpose of representing the digestibility and assimilability of various albuminous foods—the figures representing the amount of bodily ni-

trogen which may be replaced by 100 units of different nitrogenous foods; the following values are given: Beef, 104.7; milk, 99.7; rice, 88.3; potato, 78.9; wheat flour, 39.5; maize meal, 23.5.

Quite recently Albertoni and Tullio, as a result of a series of experiments carried out on three individuals, arrived at the conclusion that there is a loss of nitrogen in the organism where the human being attempts to subsist on a maize diet, and have, to all intents and purposes, revived the theories of Neusser and DeGiaxa already referred to. These writers think that as a result of the indigestibility of maize proteins the peasant who subsists on such substances must of necessity eat a larger quantity than would otherwise be necessary, and that as a consequence a considerable amount of the material passes through the intestine undigested, followed by putrefactive processes and even changes in the wall of the gut.

Passerini arrives at a similar conclusion as a result of chemical examinations of numerous samples of maize, for, it is obvious, he affirms, when we consider the amount of polenta which the average peasant consumes, that it does not contain a sufficient amount of nitrogenous material to support life properly.

Fidanza has also recently written an interesting paper, in which he agrees that there is a deficiency in nitrogenous intake in those who live wholly on maize.

Still more recently Baruttau has insisted on the small biologic value of the proteins of cereals and of peas; this author makes the interesting assertion that the plastic value of vegetable proteins is in many instances decidedly increased by the addition of the stalks, hulls and leaves of various vegetables, a fact which is quite in keeping with the demonstration of Holst and Frölich that the antiscorbutic power of dried cabbage—in which state this property is almost extinct—is remarkably increased by boiling it with a weak solution of citric acid.

From the foregoing it would appear certain that where the human being attempts to live exclusively on maize products the organism must suffer; if the total amount of this food be sufficiently great to furnish an adequate supply of assimilable nitrogen, it seems likely that indigestion resulting from an excess of the other constituents might not uncommonly result, while on the other hand if only such quantities be consumed as would furnish a sufficient amount of carbohydrates and oils, there is certainly some basis for the assumption that a nitrogen hunger might follow. It should, however, be remembered—even though we allow to the maize proteins only the low degree of biologic value determined by Thomas—that it would only require about 15 ounces of maize meal to furnish sufficient protein material to keep up a nitrogen balance for 24 hours, though this amount would be something like a third of that required, should it be determined in the future that the figures that have been accepted in the past are approximately correct. In any event, a discussion of this kind would be applicable alone to those European peasants who practically subsist on Indian corn, and would rarely or never have any

important bearing on conditions such as exist in the southern part of the United States; while it may be the case that for short periods of time the very poorest of the while people and a certain proportion of the colored population may largely subsist on corn bread and salt hog meat, it is nevertheless true that conditions of this kind are on the whole rare, and that there is a considerable variety in the dietary of practically all of our people. Among our wealthier classes such conditions may be said never to exist, since perhaps no people on the globe have a greater variety or a greater abundance of food than our well-to-do southern farmer, and it is unquestionably true that he is attacked by pellagra with extreme frequency, though perhaps not quite so often as his less fortunate neighbors.

At this point it is interesting to observe that Zuntz has demonstrated that the consumption of oxygen is increased about 25%, with a corresponding increase in the carbondioxide, in persons living on Indian corn.

Finally attention should be directed to the interesting fact recently experimentally shown by Nitzescu, to the effect that the component parts of maize are much more easily digested and assimilated when two or three years old than when fresh.

Observations Upon Which Maize Theories Are Based.

Before beginning a study of the relationship of maize to pellagra, certain general facts should be at this point considered, a knowledge of which is necessary in order that we may understand the deductive processes by which this view became current among the earlier pellagrologists.

That pellagra is a comparatively new disease there can be no reasonable doubt. All of the earlier investigators maintained that the malady had only recently become common in their respective localities, and we find very soon after its discovery the learned Gherardini (pp. 47-53) strongly calling attention to the fact that it had only a short time before made its appearance in Italy. He mentions that Ramazzini, who described with the greatest care and accuracy the diseases of the Italian peasants, makes not the slightest mention of anything that could be regarded as pellagra, and it should not be forgotten that this writer was an Italian, and was well acquainted with all classes of the inhabitants of his country. Likewise Sauvages described nothing in his great treatise on nosology which could be regarded as being even similar to this disease. Furthermore neither Plenck nor Lorry, in their works on skin diseases, made mention of any malady resembling pellagra; the former described 159 different cutaneous diseases, and the latter filled a large volume with his painstaking observations on these affections. The like is true of the transactions of the English medical societies, those of the Academy of Paris, St. Petersburg, Berlin and Leipsig, and in addition none of the earlier Italian journals speak of any malady which could be looked upon as pellagra.

While it is true that some writers, as Frapolli, have maintained that pellagra has always existed, this view was not founded on clear and patent facts, but was the result of an unwillingness to believe anything that interfered with their respective theories; the writer just referred to from the beginning assumed that pellagra is caused only by the sun's rays, and he therefore felt himself compelled to maintain that since the sun had always existed, this malady must have done so likewise. No one, however, has seriously attempted to dispute that the disease made its appearance in Europe early in the eighteenth century, and we are certainly in possession of no facts that would go to indicate anything to the contrary; it thus becomes evident that the cause, whatever it may be, began to operate about this period.

As has been before mentioned, it was remarked as noteworthy even by Casal that the staple food of the peasantry among whom this malady prevailed was maize, and the fact was likewise observed by practically all succeeding pellagrologists.

While Gherardini mentioned the unwholesomeness of bad maize, and Thouvenel observed that this cereal was the principal food of the peasants in those districts where pellagra prevailed, the first writer on this disease who distinctly enunciated the doctrine that this malady is caused by the consumption of maize was Fanzago (2), whose article on the subject, though written in February, 1807, was not published until 1809. In his discussion of a possible relationship of food to this affection, he correctly observes that there are at least two objections of great force which militate against the view that misery may stand in a causal relationship to pellagra; the first of these is that although it is unquestionably true that the inhabitants of Lombardy were only able to obtain food of the poorest quality at that time, and that this had always been more or less the case, the malady had only existed in this province for something like a hundred years at most; the second is that while the inhabitants of neighboring states in northern Italy live equally miserably, this terrible disease had not as yet made its appearance in these districts. He calls attention to the fact that there was a change in the daily food of the peasants about the time that pellagra first appeared, for at this period maize was introduced and its cultivation first became general—being in 1807 the principal aliment of the agriculturalists of this province. He quotes Bauhino to the effect that the Indians who abused this form of food became bloated and mangy. With Pimbiolo this writer agrees that while maize may appear to have excellent food properties, this does not prove that it is of relatively great nutritive value. He then goes on to say that the long-continued use of a food of this kind must lead to a gradual physical deterioration, though he guardedly adds that such deleterious influences must operate in conjunction with others in order to make the effect marked and permanent. Its injurious action, he thinks, is in a measure due to the fact that it is often harvested before being ripened and without being sufficiently dried; in fact the years are very rare in which

it attains a proper maturity and desiccation. As regards the objection that urban dwellers do not suffer from the malady, he answers that they do not live wholly and alone on polenta (pp. 15-21).

He finally concludes by remarking: "It should not, however, be deduced that we have in this the sole and only cause of pellagra" (p. 19).

The first writer who uncompromisingly connected maize with pellagra was Marzari, whose celebrated memoir appeared in 1810.

He begins by quoting the well-known aphorism of Voltaire to the effect that if a thing can only be caused in two ways and it is possible to demonstrate that this is not done by one of these, it follows of necessity that the result must be the consequence of the action of the other; of course the difficulty in this method of reasoning lies in our inability always to say the former can be excluded with certainty. As an example of the errors to which such reasoning may lead, we may refer to the fact that in Marzari's day we had no inkling of the possibility of infection through intermediate hosts—the demonstration of which has been one of the great triumphs of modern medicine—and as a consequence the deductions of this writer must be, at least in a measure, at fault. Within his limitations, however, he reasons with great vigor and clearness, and many of the facts to which he called attention are not without considerable force at the present time in connection with this discussion.

Leaving out of question the probability of the malady being hereditary or contagious, Mazari asserts that there are only two other possibilities as to its causation, which are that it may be conveyed either by the air or the food.

If the disease is due to peculiarities of climate or special conditions of the air, it would, he thinks, be present at all times, and would likewise exist in the towns and in every other place, among all classes of people who breathe it. Likewise it would be present beyond the 45th latitude, which was not the case with pellagra at that time.

Marzari believes that it cannot be produced by the sun, for it occurs without the patient having been exposed; furthermore, an infinite number of persons labor throughout their lives without shelter and never suffer any ill consequences. It is likewise true that persons living in cities who pursue outdoor occupations are not affected with the disease.

For obvious reasons it is not caused by common articles of diet, such as water and milk.

While the malady is almost confined to peasants, it cannot be true that their occupation is responsible, for the farmers in other parts of the world under similar conditions of poverty never suffer.

It is well-known, he affirms, that the tillers of the soil suffer most, and that they live almost wholly on maize throughout the winter and spring, without any meat at all. The quality of the maize used is also a matter of moment, as the "cinquantino" and "temporivo," which are the common varieties of this cereal cultivated, rarely ma-

ture in the autumn, and commonly become musty in the spring. A careful search of the records showed, according to the universal testimony of writers, that maize was not common in Italy before the earlier years of the eighteenth century—a period closely corresponding to that when pellagra first made its appearance.

Since it is out of the question that pellagra is produced by climate, by the air, dwelling in the country districts, by the method of life, or by the character of the labor, Marzari thinks it fair to assume that it must be the consequence of something eaten by its victims; as it is well-known that the only variation in their food has been the addition of maize, upon which they mostly subsist in the winter and spring, it is reasonable to assume that the malady is in some way the result of this cereal. The only weak point in Marzari's armor is the fact already pointed out that he knew nothing of the possibility of the disease being conveyed by intermediate hosts. As matters stand at the present time, however, there is not a particle of evidence that this is true, and both the symptomatology and pathological anatomy and histology loudly proclaim to the contrary. It is interesting to note that the discussion of the parapellagras, of which some of the modern parasitologists make so much capital, began with Marzari, who took exceptions to the two or three cases of supposed pellagra reported by Strambio, which were thought to have no connection with maize. Marzari pointed out that even so eminent an authority as Strambio may have made a mistake in diagnosis, and he likewise referred to the fact that this investigator may have been badly informed as to the patient's previous habits; it might be added that it was still more probable that Strambio was was not correctly informed as to the possibilities of heredity in these cases.

Marzari very well remarks that such occasional exceptions as those just referred to have but little importance, as they may be and probably are the result of error, and have no great weight where a multitude of facts point in the opposite direction. He insists that he is not discussing occasional and rare cases, but endemic pellagra in those districts of Italy where thousands yearly succumb to its ravages. He quaintly remarks:

"Thus when a million of facts have caused me to think with certainty that this particular food forms the cause of pellagra, two or three things which would appear to oppose should not be sufficient to disprove this view. Strambio did not present more than two or three observations which confuted my thesis."

This writer likewise called attention to the great influence of debilitating factors in the production of this malady, among which he says weakness is of first importance. As examples of pathologic states that may predispose to pellagra he mentions cachexias, chlorosis, the special diseases of women, grief, parturition, lactation, acid wines, intemperate use of purgatives, unnecessary blood letting, which with the "acid and hot vapors" of the stalls in which the peasants pass the entire winter, along with filthiness and concomi-

tant evil influences, become all the more deadly when combined with the vegetable diet which is denounced by this writer.

While it is true that many of the earlier observers—among whom Gherardini should be particularly mentioned—called attention to the fact that the unfortunate victims of pellagra subsist largely on bad maize products, the idea that pellagra is due exclusively to mouldy Indian corn was first distinctly enunciated by Guerreschi in 1814. In a very remarkable paper this brilliant writer pointed out the marked resemblance between pellagra and ergotism, and strongly urged the probability of the two affections being the result of related pathogenic agencies; as it was known that ergotism is produced by a low vegetable form growing in rye, this writer urged that there was no reason why moulds developing in maize should not produce similar results, with similar action on the human organism. While it is true that Guerreschi made no attempt to establish the truth of his hypothesis in an experimental way, we can not but admire the remarkable argument with which this writer, reasoning wholly by analogy, something over a hundred years ago, clearly enunciated the maize doctrine of the etiology of pellagra. It is thus seen that while the theory which accounts for pellagra as the result of the consumption of bad maize has been often associated with the name of Balardini, and to an even still greater extent with that of Lombroso, it is to Guerreschi that we are really indebted for the first enunciation of this doctrine.

Balardini (1) follows in the early chapters of his classic brochure of 1845 the same line of argument laid down by Marzari, though amplified in some particulars—these two authors together making a complete statement of the maize theory. Balardini mentions that Moscati has shown that pellagra did not exist in Italy before 1740.

Zanon says that maize first made its appearance in the markets after 1620, and Facheris asserts that the cultivation of the grain began in Bergamasco in 1632.

In Treviso the first price-list containing a mention of this cereal bears the date of Jan. 16, 1686.

Sette (2) inspected the registers of the ancient religious communities of Venice, and found the first reference to maize was about 1700; this is confirmed by Muratori. The grain was hardly known before 1710, while it did not become the common food of the peasants before the middle of the century.

Mention is made of the fact that "cinquantino" was the variety of maize commonly used by the people as a whole, and that it rarely ripened. Balardini says:

"Maize gradually drove out the older cereals and the poor peasants subsisted almost entirely on polenta (mush). This constitutes nine-tenths of the entire daily food. In order to understand the method of living in this region, let us enter the house of a peasant. We will see placed in the middle of the table a large mass of yellow dough cut into large slices, the entire family eating in a circle, with the few legumes and green things which the season allows, with

very little cheese, rarely or never fresh meat or other more nourishing aliment. Coming to the later meals we find that polenta plays the same important part, it constituting practically the only food; with it water is usually drunk, wine being only rarely added to the feast." (1, p. 40.)

He mentions that in other provinces where polenta is not so much used, a form of bread takes its place, which is unleavened, heavy, and usually acid, and the interior only partially cooked.

There is likewise, he says, a close relationship between the consumption of maize and the incidence of pellagra. Thus it is true that most maize is eaten in the Provinces of Bressica and Bergamo, and that here the proportion of pellagrins is much greater than in other parts of Italy. Likewise in the upper districts of the Milanese territory pellagra is very common, and the food of the peasants consists almost exclusively of mush. In the Province of Venice we find great quantities of maize eaten, the variety being usually known as "quarantino," and which rarely matures, and here it is, according to Zecchinelli, that one-sixth of the peasants have the disease.

The same condition of affairs exists in the country north of the Po, where this cereal is much eaten and pellagra is frequent.

In the Piedmont the grain is much cultivated and pellagra is almost as common as in Lombardy. In the Val d'Aosta many of the communities principally subsist on maize, making with it a bread called "miasse."

Pellagra is also common in Mugello and Pistogese.

In the mountainous regions of Biella, however, pellagra is rare, though much maize is eaten. The local physician, Curiotti, explains this fact by the statement that here the maize is of perfect quality, and that, furthermore, almost all of the men remain away from their homes for the greater part of the year, being employed in the construction of streets and other public works in various cities.

It is likewise true that in the Province of Cremasco pellagra is rare. The inhabitants, however, lead a wandering life, engage in traffic and smuggling, and have much better food than the average peasant.

In lower Lombardy the disease is less common, but on account of the richness of the soil the peasants there have other foods.

In the Province of Domodossola pellagra is unknown, nor do the peasants eat maize.

In the Genovese coastal regions pellagra is rarely seen. The inhabitants eat but little polenta, and have a varied dietary. The disease does not occur in southern Italy, or to any extent in Sardinia, where maize was at that time not eaten.

From Monjovet on to Courmayeur, and thence to Thuille, pellagra is not seen, and here the peasants live largely on chestnuts and other foods, though some maize is eaten. It is likewise said that the disease prevails in the Val d'Aosta to a certain extent, where chestnuts are largely used for making bread.

In western France, in the provinces of Gascony and Landes, where pellagra occurs to a considerable extent, the principal food, according to Bonafous, is almost exclusively maize bread.

At that time pellagra occurred in Europe only between the 43rd and 46th parallels of latitude.

The Valtellinese of Lombardy live in a low and humid locality, in poorly ventilated dwellings, and formerly subsisted on rye bread, and a black dough made from the *Polygonum fagopyrum*, to which they added a little butter and cheese, and a few vegetables; they remained healthy, it would appear, until maize was introduced, and this was followed by the development of pellagra.

The inhabitants of Sandris are exposed to the same general conditions as those just referred to, though maize has never been introduced, likewise pellagra has never appeared. In the Commune of Aborno maize constitutes the entire diet; pellagra, under the name of "salso," is frightfully prevalent.

Balardini states that mill operatives are immune.

Giuseppe Cerri (2), in 1795, provided ten evident pellagrins with good food, which was continued into the succeeding year, and he had the satisfaction of seeing that their general condition was greatly improved and that in no instance did the disease develop in the following spring. Others have repeated this with practically the same results, among whom were Balardini and Vajarini.

Sons of pellagrous parents are unhesitatingly accepted by the military authorities, as it is the uniform experience that they grow stronger under the more sanitary conditions and better food of the army. In this connection a case of Cerri's is interesting. The patient, a peasant, was assailed with violence by pellagra; he changed his occupation to that of a family servant, and shortly recovered. Believing himself well, he returned after a time to his former occupation and food, consisting mainly of polenta, and in a short time was again attacked by his old trouble. He then returned to his position as a servant and regained his health, but lost it on going back again to his labors in the field. Being now convinced of the necessity of giving up his peasant life, he returned to the family who had before taken care of him, regained his health, and lived to the age of 86 years.

That maize is not eaten with impunity, even in Mexico or in Guiana, where the grain matures, is held by Bauhino, who in his celebrated "Theatrum Botanicum," mentions that the natives of Guiana who eat this cereal frequently have skin eruptions. Hernandez, who was sent by Philip II to America to study its natural history, declares in his authoritative work on this subject that among the original inhabitants of Mexico maize was evidently not as nourishing as wheat. DeSolis is of the same opinion, and states that those who eat this cereal habitually suffer from a cutaneous malady known as "ressori." Tissot thought that the physical and mental inferiority of the people of New Spain was the result of eating maize, and states that Indians acquire as much vigor as their European

brothers so soon as they begin to subsist on wheaten bread; this observation is confirmed by Humboldt. It is interesting also to observe in this connection that Vales, in his interesting brochure on pellagra in Yucatan, observes that all of the Indian tribes have separate and distinct names for pellagra, which is common among them, and from which he deduces the antiquity of the malady in those regions. G. P. Franck (2), in his classical work on diseases caused by misery, states that maize products are indigestible, that they ferment and become acid and produce all sorts of dyspeptic disturbances, and, as a consequence, atrophies, rickets and convulsions.

Geoffroy speaks to the same effect.

It should also be remembered that in America maize is often affected by smut (Uredo maydis), and that in Colombia it is thought to cause a disease popularly known as "pelatina," resulting in loss of the hair of the head and body, and falling out of the teeth and finger nails.

While it is true that the beliefs of the writers of the last century were with but few exceptions founded on general observation, and had no very substantial basis in direct proof, it is of historical interest that an overwhelming percentage of those who recorded their views held that maize was in some way responsible for pellagra. Leaving out of consideration the great leaders on the affirmative side of this discussion, such as Fanzago (2), Marzari (1-3), Guerreschi, Balardini (1, 2), and Lombroso (2-11), in Italy; Roussel (2, 3) and Costellat (1, 2), in France; Neusser (1, 2), in Austria, and Babes and Sion (2), in Roumania, we find that the following eminent writers expressed themselves in favor of the maize theory, they having written in the order mentioned. Among the Italians, so thought Chiarugi, Moris, Sette (2), Giovanni Strambio and Ambrosoli, Triberti, Mastri, Manassei, Tuccimei, Klein, Girolami, Dupré, Erba, Brugnatelli, Selmi, Sacchi, Bassi, Palmesi, Cavagnis, Ercolani, Fritz (1, 2), Majocchi (2), Bordoni, Uffreduzzi and Ottolenghi, Camillis, Meragliano, Longhi and G. B. Verga; in France, Gintrac, Raymond, Tardieu, and Poussié; in Corfu, Typoldos; in Germany, Husemann and Hofmeister; in Austria, Kluczenko, Berger, Merk (2), and the Government Commission consisting of Niederman, Konrad and Farkas, and Procopiu of Roumania, were of like opinion, though many of these writers believed that bad food and unhygienic conditions are potent factors in the production of this affection.

It may be noted that the closest possible connection between pellagra and the habitual eating of maize has been consistently claimed by nearly all modern observers who have given the matter most attention—of which more will be said in the succeeding pages. It may be mentioned here that it is well-known that pellagra in this country is closely confined to those areas where this cereal is commonly eaten, with only trifling apparent exceptions, which may well be accounted for by possible errors in diagnosis.

In Italy the latest statistical study is that of Camurri (8), who found that of 1,300 pellagrins personally observed, all, without exception, were eaters of Indian corn.

We will now examine *seriatim* the different theories that have been advanced which connect maize with pellagra. Inasmuch as the majority of these can scarcely be looked upon as more than pure speculation, and have only a certain amount of historic interest, we will not attempt in these pages to consider them in the order in which they were evolved; we will take up first those that are evidently of but little or no importance, and lastly deal with such as appear to be worthy of serious consideration.

MAIZE SMUT (UREDO MAYDIS) THEORY (PARI, 1870).

According to Pari's theory, pellagra is due to the common parasite frequently found on maize, which is known in common parlance as "maize smut" or "maize brand" (Uredo Maydis; Ustilago Maydis). However, it is not assumed, as one would naturally suppose, that this parasite is mixed with the maize at the time of harvesting, but rather that it is carried to the homes of the peasants in various ways, where the spores being constantly present, inoculate the meal, the dough, and the bread. Having been taken into the body, the spores furnish, along with the substance of the maize, a sort of tinder or combustible material that circulates in the blood, and catches fire, as it were, when the patient goes in the sun, occasioning a sort of internal combustion, with the production of all of the symptoms of pellagra. The reason that pellagra is more common among the peasants is that the number of spores of this fungus is naturally much greater around their simple habitations than in the homes of the well-to-do, and that those who labor in the fields are necessarily more exposed to the sun's rays.

UNLEAVENED BREAD THEORY (FAYE, 1880).

A number of years ago Faye conceived the idea that pellagra is due to the fact that maize products are almost wholly consumed in an unleavened state. It does not appear, however, that anyone has subsequently seriously considered this view of the causation of this affection. At the present time the theory has only historic interest.

THEORIES OF IMPERFECT DIGESTION OF MAIZE PRODUCTS (NEUSSER, 1887; DEGIAXA, 1902).

While it has been assumed by many from the earliest days of the study of pellagra, that maize products are indigestible, and therefore conducive to the development of this disease, the idea was first elevated to the dignity of an etiologic doctrine by Neusser (1, 2) in 1887. Observing that those most subject to this affection are generally below the average physically, and are not infrequently dyspeptics, it occurred to this very capable investigator that we might account for pellagra on the theory that certain component parts of maize are thoroughly digested and assimilated without harm by the normal organism, but that where this does not occur and the material is only imperfectly acted upon by the ferments of the digestive tract, it becomes a sort of mother substance to chemical bodies that are poisonous ,and which, if continually taken for a long period of time, may ultimately give rise to pellagra. Unfortunately Neusser made no experimental investigations with the idea of determining the truth of this speculation, and the theory, therefore, has not attracted any considerable attention.

Somewhat different from the view just referred to is the theory advanced some years later by DeGiaxa (1, 2); observing the fact, which is quite well substantiated, that the albuminous portions of maize pass through the intestinal tract in greater proportion than do the corresponding nitrogenous bodies of other cereals, it was assumed by this writer that, since it is well-known that such

materials act as culture media for bacteria, it is reasonable to assume that there would be a corresponding increase in these organisms in the intestine, with the production of a greater amount of toxic substances than is normally the case. He would, therefore, assume that the maize eater is the subject of a chronic intoxication of a character more pronounced than is the case in healthy people, and that a continuation of such conditions for a long period of time may ultimately result in the production of pellagra. It is interesting to observe that this writer and his students offered, as proof of this theory, experimental data that indicate that the colon bacillus becomes particularly virulent in animals fed on maize products, and that the number of these organisms vastly increases.

It is also interesting to observe that fundamentally these views are by no means new, since Videmar, in 1790, suggested that the bad quality of the foods usually eaten by pellagrins causes imperfect digestion, and that as a result the blood becomes "vaporous, watery, and acid" (p. 70), and that in the following year Soler says that "the bad foods produce in the stomach the pellagrous poison" (p. 43).

It can scarcely be doubted that the influences suggested by these writers act at least as predisposing causes in the production of pellagra.

Mixed Good and Mouldy Maize Theory (Gherardi, 1905).

Some years ago Gherardi advanced the idea that the milder forms of pellagra are due simply to eating ordinary maize, while the severer types of the affection occur only in those who are in the habit of eating the cereal in a mouldy state. While no one else seems to have accepted this view, it is of interest in connection with certain recent investigation. While no one else seems to have gone so far as definitely to claim that the consumption of sound maize alone is capable of causing pellagra, it is of interest to recall that it has been suggested that the grain may contain pathogenic ferments, and that its zein is mildly toxic; moreover the evidence is now conclusive that the cereal is an imperfect food and can not be used as the sole aliment without serious consequences to the health—a fact long ago observed by the early investigators of the subject.

Photodynamic Theory (Aschoff, 1908; Horbaczewski, 1910).

As pointed out by Darwin, it has long been known that in some parts of the world white hogs or sheep rarely survive early life, this being a consequence of their eating certain plants; one of the most curious and interesting results of scientific investigation is the demonstration of the fact that this is brought about by the action of certain bodies—called photodynamic substances—that have the property, when circulating in the blood of an animal, of being so affected by the chemical rays of light penetrating its skin that they become toxic and produce local lesions in its tissues. Naturally when the animal is shielded from the rays of light by artificial coverings no effects are produced, and for the same reason where the skin or hair is dark the chemical rays are broken up before entering the deeper tissues and no ill consequences follow. We are then confronted with the singular fact that the color of an animal determines whether or not certain substances shall act as poisons to it—provided always that exposure to light be at the same time permitted. The work of Tappeiner and others is based on these facts.*

The experimental demonstration of the action of such substances on animals was first made by Oehnke, in 1909, he having operated with mice and guinea

*Space does not permit a complete discussion of the steps by which these demonstrations were made; it may be, however, briefly said they had their origin in some experiments made by Raab in the winter of 1897-1898, at the suggestion of Tappeiner. This investigator found that there is great variation in the action of acridin—a fluorescent substance—in its action on *parameciae*, and it was ultimately determined that this is the consequence of some days being cloudy and others bright at the time the experiments were being carried on. The whole subject was then thoroughly investigated by Tappeiner, and Tappeiner and Jodlbauer. (Die Sensibilisierende Wirkung Fluorescierende Substanzen. Leipzig, 1907.)

pigs to which he fed buckwheat, and was able to produce in such as were white the same symptoms that had been observed under natural conditions in sheep and swine of the same color after consuming the seeds of this plant.

This work was followed up in 1909 by Fischer, who wrote an exceedingly interesting and carefully prepared paper on the subject, in which he proved that the photodynamic substance is a fluorescent constituent of the hulls of the buckwheat grains; this observer showed that this substance may be extracted with alcohol, ether, or chloroform, and may be obtained from these reagents in the form of needle-like crystals. It is important to remember that only traces of this poison were found by the author just mentioned, in the buckwheat of commerce, it being removed along with the husks, and it is, therefore, not strange that we have no well authenticated instance of poisoning of this kind in the human being. True, Smith has reported a case where a patient always suffered unpleasant symptoms immediately after eating buckwheat, but it is clear that there could be no question under such circumstances of photodynamic phenomena. As the poison just referred to is the only toxic substance known to exist in this plant, the assumption is gratuitous that this case should be looked upon as one of buckwheat poisoning in the restricted sense in which the word is here used; this curious instance of hypersensitiveness belongs, on the other hand, rather distinctly to that bizarre group of cases in which remarkable intolerance exists in some individuals to even the smallest traces of certain foods or drugs, and which forcibly bring to mind the symptoms observed in anaphylaxis. The two cases quoted by Smith as having been reported by Rakun, of St. Petersburg, are likewise doubtful, being more probably the result, as the Russian author himself thought, of a mixture of henbane with the buckwheat.

In 1908 Aschoff, being thoroughly acquainted with the facts just referred to respecting the photodynamic power of some substance in buckwheat. suggested that pellagra might be due to a similar poison in maize, and this was shortly followed by a series of articles by other authors advocating this view.

As the result of experiments on mice Horbaczewski, in 1910, arrived at the conclusion that the coloring matter of maize is a photodynamic poison, and that often, independently of association with light, this constituent of Indian corn is more or less toxic. In the same year Raubitschek (1) arrived at similar conclusions, he being of the opinion that the poison is a lipoid.

Hausmann fed white rabbits on maize, and then produced reactions on their skin by exposing them to light.

Other articles on this subject, confirmatory of those already referred to, were written in 1911-1912 by Raubitschek (2, 3), and in the latter year by Horbaczewski. It is noteworthy that the latter writer was able to produce symptoms of photodynamic poisoning in mice by the administration of maize from which all of the zein and coloring matter had been extracted—which results by no means confirm the investigations already mentioned.

There is not wanting, however, experimental evidence which seems to contradict the theory that maize contains photodynamic poisons. Thus we find Hausmann calling attention to the fact that animals in large numbers eat maize and are at the same time exposed to light without any trouble resulting; he also refers to the fact that while hogs are susceptible to the poison of buckwheat, no symptoms follow when they consume maize. According to this writer also the symptoms and lesions in pellagra and those produced by light are different, there being with the latter intense itching and necrosis, neither of which occurs in the former disease. He also notes that pellagra does not come on at the period of the year when the rays of the sun are strongest.

Sormani conducted a series of experiments with the object of confirming those of Raubitschek, but after very careful investigation, arrived at the conclusion that there was no evidence of photodynamic poisons in maize. He says:

"Good maize produces nothing more than a slight diminution in weight in white mice in whatever way it is administered as food, and quite independently of whether the animal is kept in the light or in the dark. Maize of bad quality reacts gravely on the nutrition of the animals and leads to their death, whether they be kept in the light or in the dark."

This writer also gives his method of extracting the lipochromes from maize. This substance appeared toxic when fed to animals, dissolved in olive oil, but

the conclusions which would naturally follow are more or less vitiated by the fact that similar symptoms followed when these animals were fed on olive oil alone.

In 1912 Hirschfelder published an interesting communication, in which he showed that the serum of normal individuals has a certain fluorescent power, and that this fluorescence is no greater in pellagrins than in healthy people.

Babes (3, 4), in two of his latest papers, objects strongly to the photodynamic theory as applied to pellagra, remarking that in those exhibiting skin alterations a careful examination always shows previous evidences of the malady.

Carbone and Cazzamolli have recently investigated this subject and entirely failed to obtain any evidence of a photodynamic substance in maize.

On the other hand, Umnus maintains that pellagra and maize poisoning in animals are identical, and that an alcohol-soluable toxin and a fluorescent yellow pigment are the pathogenic agencies. He specifically maintains that pellagra is a result of photodynamic substances.

To the experimental and other objections urged against this theory must be added likewise the well-known fact that the blackest negroes in America suffer quite as much, if not more, from this affection than do the whites. Whatever results may be apparently obtained by experiments on animals, it may be said that all of the important facts tending to show a causal relationship between maize and pellagra would seem to invalidate this view, and would indicate clearly that the propounders of this theory possess only a superficial and very inadequate conception of the malady; most certainly without great modification it could hardly be entertained by anyone acquainted with the subject.

VITAMINE THEORY (FUNK, 1914).

Of possible interest in connection with the etiology of pellagra are some very remarkable observations which have been made, particularly by students of beri-beri, a disease that has long been known to have a relationship to the consumption of rice, and which in many of its clinical manifestations presents marked resemblances to the phenomena encountered in pellagra. That beri-beri was in some way the result of rice consumption was first suggested by Wernich, and that the conjecture had a solid basis was shown only a year or so later when Takari, in 1882, caused the malady to practically disappear from the Japanese navy by changing the diet from one almost exclusively of rice to a mixed regimen. Notwithstanding this clear demonstration, there was a vast number of writers who denied the connection, and we find here the same pestilential theorizing and utter ignoring of facts which has already been noticed as one of the characteristic features of pellagra literature.

In 1897, however, a new light was shed on the whole subject when Eykman made the capital discovery that only such persons as live almost exclusively on polished rice became victims of beri-beri, and this investigator then naturally assumed that some most important constituent was removed with the hulls of the cereal. It was later shown by Fraser and Stanton that at least one of the protective substances lies just beneath the husk, and it has been found by Casimir Funk that it may be obtained in a more or less pure state by chemical means, and that solutions of it constantly give, in a modified way, the reaction, discovered by Folin and Maccallum, which results when alkaline solutions of phosphomolybdic or phospho-tungstic acid are added to solutions of uric acid. *

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*This reaction has been recently employed by the above named writers for making quantitative examinations for uric acid, giving when this substance is present a purplish hue. It is carried out as follows—two solutions being required:

The first is prepared by boiling for a couple of hours 100 grams of sodium tungstate with 80 c. c. of 85% phosphoric acid and 750 c. c. of water, the whole being diluted to one litre after cooling.

The second is simply a saturated solution of sodium carbonate.

In making the test the phospho-tungstic acid solution is first applied to the decorticated surface of the grain to be tested, to be immediately followed by an application of the second solution. Should this test prove to be characteristic, it would be doubtless possible to estimate accurately the amount of vitamines in a definite quantity of any cereal, though of course, under such circumstances the cereal vitamine would have to be suspended in some solvent.

The exact method of action of these peculiar substances, called by Funk "vitamines," is as yet very uncertain, but that they play a most important part in the economy of nutrition there can be no question. Fortunately they are present in practically all foods, so that the likelihood of their being deficient in any given dietary of a mixed character would appear to be small. Where, however, persons live almost exclusively on one cereal, the danger of poisoning from lack of vitamines is much greater, particularly where the husk is separated and removed before the grain is eaten. Funk has recently advanced the theory that pellagra is produced in this way, he assuming that those who become pellagrous habitually subsist on husked Indian corn. How far the facts bear out this theory in the old world the writer is not in a position to say definitely, but that there would appear some basis for this conclusion in America, he thinks there can be no question. It is a well-known fact that in the maize eating portions of the United States the great bulk of the population was formerly served by small water-mills, and that the meal obtained from their maize contained a very large percentage of the husk; it is likewise apparently the case that pellagra was much rarer in the past, and that when it did occur it was probably of a much milder type. At the present time, however, the small mills just referred to have been in a large measure replaced by much larger manufacturing plants, and the roller has taken the place of the old-fashioned mill-stone, with the result that much of the meal now eaten is almost completely decorticated and at the same time degerminated. On the other hand, there are apparently insuperable objections to the acceptance of this theory—chief among which is the fact that the American pellagrin always subsists on a more or less mixed diet. It is possibly true that here and there among the very poorest classes the average meal may at certain seasons consist only of maize-bread and bacon, but this is far from being the rule, and practically without exception, even among the most poverty stricken, there is variation in the quality of the food from day to day. It, therefore, seems almost certain that in an overwhelming majority of cases if the bread of our people is not sufficiently supplied with vitamines they obtain the necessary amount of such substance from other foods. As another objection to this theory may be urged the fact that it is precisely in those regions where the old-fashioned rock-mill is still to be found that pellagra is most common.

In this connection it is interesting to observe that the Folin reaction is not limited in maize to the outer portions of the grain, occurring particularly in its softer portions, and that the tint produced by his reagent is not violet but blue.

There can be no reasonable doubt, as interesting as it is, that this theory will be found inadequate to account for pellagra, as most of the known facts are strongly against it.

FERMENT THEORIES (SELMI, 1876-77; ROMARO, 1908; CAMURRI, 1910).

One of the most interesting and suggestive books that has appeared on the causation of pellagra since the publication of the great work of Balardini is that of Romaro (1, 2), and whatever may be the ultimate fate of the theory therein put forward, there can be no doubt that it has reopened a field of investigation which is most inviting, and that it offers explanations, especially in some particulars, of the clinical facts that can not fail to arrest the attention of the student. Inasmuch as this theory was in all essential respects proposed many years ago by the celebrated Selmi, and as Romaro could scarcely have been ignorant of this, it is much to be regretted that the latter writer did not give proper credit in his book.

Briefly, it is assumed that the morbific substance or substances that give rise to pellagra do not occur in maize except in the spring, at which time they are formed as the result of germinative changes ,and have no relationship to the action of low vegetable forms of any kind.

While the writer adduces no experimental evidence of the truth of his views, he certainly makes a most interesting case by reasoning from analogy. He points out that in the animal kingdom certain well-marked alterations take place in both the male and female at the beginning of the rutting season, and there occurs even more pronounced changes in the vegetable world. He says:

"We observe that vegetables and animals exhibit in the spring, or in the period of their love-making which is not at the same season, metamorphoses which are the result of the act of reproduction of the species.

"In both animals and vegetables—and in some this change is very active—such alterations occur as to produce new substances capable of altering the health of those who eat them as food.

"It is very easy to admit and comprehend how much influence, how much power, and how much force are elaborated by nature in animals and vegetables in the spring, and what intimate and hidden depths are stirred, what perturbations are caused in all animate things, from the braying of the ass as it salutes the May morning, to the pellagrogenic substance of Indian corn. In this season the seeds of trees and of plants begin the act of germination, and in preparing for this important function chemical changes occur which give rise to new products, new molecular changes, and new combinations, some of which are poisonous."

He calls attention also to the fact that a number of animals and fishes are poisonous during the rutting or spawning season.

Of great interest in this connection is his reference to *lupinosis*, which is quite frequent in Germany. This is a disease of cattle caused by eating the *Fava lupina*, and it is the case that lambs born in January and February develop the affection after weaning toward the middle of April. This writer quotes Haubner as saying that lupines may be left for a long time in the air, especially at low temperatures, without showing any alteration, but that they become poisonous quickly when kept in granaries or silos.

Without any very definite reasons for his view, Romaro is strongly of the opinion that the supposititious toxic substances are enzymes—in which he clearly follows the view previously put forward by Selmi. In this connection it should never be forgotten that the latter investigator showed in 1876-77 that there is produced in germinating maize a ferment closely related to diastase, and which was called by him *zeastase*. This ferment was shown by Selmi to produce marked alterations of a chemical character in maize meal which had been made into dough. This acute investigator observed that the addition of acids or alkalies rendered musty meal sweet and good—this effect largely resulting, as shown by him experimentally, as a consequence of the destruction of the zeastase.

When it is considered that germinative changes could only occur in maize which is comparatively sound, Romaro's theory is directly opposed to that of Balardini, the assumption being that the better the grain the more likely it is that it will produce the disease.

Romaro remarks that the most satisfactory method of preventing pellagra consists in desiccating the maize, and he assumes that in this process the temperature is carried up, as a rule, sufficiently high to destroy any enzymes that might be present, it being well-known that these substances decompose somewhere between 100° to 170° C.

Notwithstanding this author's insistence on the idea that ferments constitute the pellagra poison, he produces no facts or reasoning which would not apply just as well to some other toxic agent.

It having been clearly shown by Bourquelot and later by Comus, Girard, Gavina and others that enzymes are abundantly produced in maize during the growth of moulds, it has been recently assumed by Camurri (4, 7, 8) that pellagra may after all be the consequence of a direct poisoning by such substances. It was noted by Gavina (4) that the methods employed by various experimenters for obtaining the toxines from mouldy maize are precisely those that are most available for separating enzymes. This writer likewise confirmed the experiments of Roussy, Loper and Esmonet respecting the toxic power of ferments when injected subcutaneously. Likewise Camurri demonstrated many enzymes in bad maize products, and does not hesitate to maintain that they are the *active pellagrogenic agencies* when introduced into a system depleted from a long continued dietary poor in sodium and lime. This investigator thinks that these ferments are absorbed, but that in the normal body they are destroyed; on the other hand, when the tissues are weakened and the digestion abnormal as a consequence of eating bad foods—among which might be an exclusive diet of maize—the enzymes pass into the general circulation and produce disease. It is not necessary that these substances enter alone with this aliment, since they

might be obtained from other foods. This writer notes that the subcutaneous administration of pepsin and pancreatin produces at first a diminution and later an increase in leucocytes, with a decrease in the red cells of from 100,000 to 700,000.

It is thus seen that the two theories, according to which ferments are responsible for pellagra, differ quite fundamentally; according to Romaro the cereal must be in sufficiently good condition for the normal processes of germination to begin—thus precluding any great amount of mouldiness—while on the other hand, according to the hypothesis of Camurri, the grain should be in an advanced state of decomposition for its maximum toxic effect to be exercised.

It is interesting to note that Gavina has shown that the normal grain contains ferments; if, therefore, there be any truth in the possibility of such substances being absorbed and producing poisonous effects, perfectly sound maize might be capable of exercising pathologic changes if the grain were taken to excess.

MONOPHAGISM (MORELLI, 1855).

According to Dönhoff, who repeated and confirmed the earlier experiments, Magendie observed somewhere about the middle of the last century that animals quickly succumbed when fed exclusively on one food, and the view that such influences might have a connection with the etiology of pellagra was distinctly put forth by the Piedmont Pellagra Commission, of 1847 (p. 65).

Apparently in ignorance of the fact that the idea was not new, Morelli, in 1856, clearly enunciated the doctrine of monophagism in explanation of pellagrous phenomena, but it appears that his speculations respecting this matter have been long forgotten.

More recently it was shown by Antonini that when dogs are fed simply on vegetables, phenomena resulted resembling those produced by an exclusive maize diet; such vegetables are cabbages, rape, potatoes or beans, mixed with fats in order to render them appetizing. After living on such a diet for some months the animals become lean, lose their hair, show symptoms that appear to result from vertigo, and have diarrhoea, vomiting, and exaggeration of the reflexes.

Somewhat later Bezzola showed that an exclusive maize diet is not sufficient to nourish properly guinea pigs, though its bad affects are much ameliorated by mixing with it other foods; both good and bad maize produce similar effects.

Audinino (8) was likewise able to produce symptoms in animals by feeding them exclusively either good or bad maize; with the former the principal phenomenon observed was a depression of temperature, while with the latter there was fever, intestinal disturbances, and falling out of the hair.

Later still, Ballner conducted a series of similar experiments, using polenta, groats, whole wheat, cooked decorticated maize, and oats—the result being that in all instances the animals ultimately died; those fed on polenta died most quickly, and those on oats last. The principal phenomena observed were loss of weight and gradual inanition until death followed, these being only rarely accompanied by skin symptoms. Ballner does not think that these effects are produced from lack of nourishment or from eating bad food, but regards the process as being one of autointoxication.

More recently Centanni and Galassi, and Centanni (2) alone, have discussed this theory, and have expressed the opinion that in addition to the toxic effects caused by maize it is likewise probable that those who live practically alone on this cereal suffer as a consequence of some elements necessary for nutrition being absent.

Although some recent writers have appeared to regard the phenomena produced in animals by monophagism and vitamine hunger as being identical, it is quite clear that they in all probability materially differ; there is some evidence, however, which would indicate the possibility that the symptoms that follow monophagism may be the consequence of an inability on the part of the organism properly to carry on metabolism unless it receives, from time to time, vitamines from radically different sources.

From the foregoing it would appear that although maize contains a high proportion of all of the food elements usually found in cereals, there is little

room to doubt that some of these are far from wholesome, and indeed it seems quite likely that under certain circumstances they may even act as mild poisons. Not only does it appear that a part of the vegetable protein of maize is mildly toxic, but there is reason to believe that there are other substances present in this cereal which act in a similar manner, though their exact nature is not as yet fully determined. Practical experience and experimental investigation concur in indicating that particularly the nitrogenous material of this grain digests badly, and that its steady consumption must, therefore, lead to forms of intestinal putrefaction. Finally, and perhaps most important of all, the varieties of this cereal grown in the United States have steadily deteriorated, with the result that the grain universally consumed at the present time is practically never free from moulds, and contains the corresponding toxic substances which these organisms are now known to elaborate.

It is thus seen that altogether outside of those morbific influences that perhaps operate with greater or less intensity in all cases where an animal organism is maintained for a long period of time on one food alone, we have, where maize forms such a dietary, abundant grounds for the belief that the effects produced would likely be much more deleterious than where any other common food is used. Does it, however, seem likely that a disease like pellagra would result from monophagism alone? It would appear not. If such terrible consequences could follow, why do we not have this malady common in China, India and many parts of Europe where the peasants subsist almost wholly on one food alone? Why does the affection frequently occur in the well to-do and even rich American who has always had a greater variety of food than corresponding classes anywhere else in the world? Can we believe that monophagism could produce the characteristic symptomatology and morbid alterations always found in pellagra? Finally, is it within the range of probability that such a morbid state could be hereditary? The answer must be, no.

Theory of Inanition.

There can be no doubt whatever, as has been already stated, that inanition and bad hygienic conditions play a most important rôle in the production of classic pellagrous attacks. So close indeed is this evident connection that Fanzago mentions in his monograph written in 1789, that the disease was called "mal della miseria" by Vaccari, and practically all of the early and many of the more modern pellagrologists have seriously contended that such influences are of the first importance in the causation of this affection. Thus Casal and Thierry, in Spain; Strambio, Gherardini, Frapolli, Zanetti, Odoardi, Albera, Sartago, Della Bona, Ghirlanda, Facheris, Nardi, Videmar, Fanzago, and others, in Italy, and Roussel, Marchant, Hammeau, and others, in France, united in testifying to the fact that the great majority of pellagrins come from the poverty stricken classes, and bad or insufficient food was all but universally regarded as the determining factor in the production of the malady during the greater part of the last century.

Although the possibility of such a connection was mentioned by nearly all of the early writers, Soler was the first to advocate unreservedly the theory (p. 5).

Facheris first distinctly enunciated the idea that the disease is caused by lack of animal food (p.. 60); however, before him Soler had advised the use of proteids in the treatment.

The first writer who adduced experimental proof that connected this affection with improper food was the celebrated pellagrologist, Giuseppe Cerri (2), who in 1795-96, urged on by the authorities of Milan, placed 10 pellagrins on a full and adequate dietary, continued feeding them in this way for a year, and had the satisfaction to observe at the expiration of this period that their general condition was greatly improved, and that in the following spring none of them showed the pellagrous symptoms from which they had previously suffered annually. Many investigators, including Balardini, repeated experiments of this kind in the early part of the last century, with similar results.

So well established was the knowledge of the effect of good food in pellagrins that the Italian Royal Commission having charge of such matters, never hesitated to declare children of families notoriously pellagrous fit for military duty, even though the pellagraderms had previously made their appearance; under such circumstances it was well-known that the young soldiers, under the improved hygienic conditions, quickly lost all signs of their disease, and almost invariably continued in good health until they went back to their former method of life. It was likewise shown by Gasparini that pellagra is by no means so common in the peasant after he quits the fields and becomes a mill operative. Also Antonni (2) and others have shown that pellagra and the price of grain in Italy simultaneously increase and diminish.

We may here again refer to the interesting example of the effect exerted by good feeding reported by Cerri, and mentioned by Nardi. A peasant who was violently assailed with the symptoms of pellagra, left his home and entered into service as a servant in the house of a family of quality, and in a short time entirely recovered. Believing that he was well, he returned to his former occupation as an agriculturalist and to his old method of life, subsisting largely on polenta and yellow bread, and in a short time was again attacked by his former trouble. He then returned to his position as a servant, and, regaining his health, again went back to the fields, but became pellagrous in a short time. Being now firmly convinced of the necessity of permanently changing his method of life, he returned to the good family who had taken care of him and regained his health and lived to the age of 86 years.

The early literature of pellagra is filled with examples of the happy effects on pellagrins of improved hygienic conditions, and especially the substitution of good food for that usually employed.

Fanzago (2) and after him Marzari (1, 2, 3), who is generally looked upon as the father of the view that the consumption of Indian corn is responsible for pellagra, were entirely of the opinion that the deleterious influences of this grain are wholly the consequence of its supposed low nitrogen content, and their view as a consequence, is nothing more nor less than that this disease is the result of proteid inanition. It is true that more thorough analyses subsequently disproved the idea that maize contains less albuminous food than other cereals, but there may be something after all in their view, for recent investigation has thrown considerable doubt on both the digestibility and food value of the nitrogenous portions of this grain—particularly that part that is called zein. Notwithstanding that the writer last referred to was in reality an exponent of the view that maize produces pellagra as a consequence of its low food value, the idea that this affection is really one that results from starvation seems generally to have been associated with the names of Morelli, and particularly Lussana and Frua, all of whom very strongly urged this view with an ability and scientific acumen that has perhaps never been surpassed. On pages 122-125 of Lussana and Frua's well-known monograph, these careful and accurate writers say:

"We recognize misery and the life of the country as being together the elements which ordinarily cause pellagra.

"Likewise their ordinary food contains an insufficient quantity of protein.

"The disease is not contagious.

"The atmospheric changes, the quality of their habitations, and the care of their bodies have no influence in the production of the disease, further than that a bad climate may interfere with the growth of vegetables, and thus indirectly act as a cause of pellagra.

"The rays of the sun bring out and increase the severity of the disease and influence in a special manner the skin alterations and vertiginous sensations.

"Excessive fatigues and mental worries favor the development of the malady.

"Ergotism (vederame) of maize has a marked influence on the causation of the malady.

"Pellagra is hereditary, whether it be that it passes directly from parent to offspring or there be on the other hand simply a transmitted organic predisposition.

"Pellagra spares no temperament, nor any particular constitution.

"The affection is most apt to follow depressing physical influences, such

as nursing, pregnancy, the puerperal state, continued fevers, chlorosis, the abuse of purgatives and blood letting, and excesses in wine and women.

"Pellagra appears to be more frequent in women, and begins with them early in life. * * *

"Pellagra develops in the midst of privations and misery, and may, therefore, be called the *morbus miseriae;* it attacks by preference the peasants, and among them the poorest, who, while subsisting habitually on maize, commonly badly conserved and musty, and on sour milk, are not sufficiently nourished to endure the fatigues of their work and the painful affects of the sun."

It is thus seen that although these writers accord to misery and inanition the first place as an etiologic factor in the production of pellagra, they likewise admit that the occurrence of the disease is influenced largely by other agencies.

If this be granted, pellagra could hardly be looked upon as a disease *per se,* and should be rather regarded as a symptom-complex.

Following the publication of the monograph of Lussana and Frua a number of writers on this subject have, to a greater or less extent, adopted the views of these authors. Thus we find that while Boudin thought pellagra caused by misery, Bouchard (1)—who knew little of the endemic disease—considers the malady due to inanition and the action of the sun; Robolotti thought that it is a consequence of fatigue and bad food, while Millot ascribed it to misery and maize eating; Winternitz and Kalindero look upon it as coming from bad hygiene; Bonfigli (1) thinks that it results from the exclusive use of maize in the winter, and that the grain, on account of being badly preserved, is indigestible and generally deleterious; Manzini was of the opinion that lack of albuminous food gives rise to the affection; Scheiber suggests that in addition to misery there is perhaps an inherited predisposition; a similar view has been recently expressed by Camurri (6), but he thinks the malady is more directly due to a demineralization, due to lack of such substances in the food, combined with an increased loss of chlorides with the urine, associated with enzyme poisons ingested with mouldy maize; Terni (2) thinks that there is also some infective agent as yet unknown; Martinelli and other writers have frequently noted that pellagra followed famines and inundations; Gavina (3) and later Reed have affirmed that the bad effects of mouldy maize are largely due to the destruction of the starchy and nitrogenous elements of the grain by the hyphomycetes, in addition to any poisons that might be produced; we should also remember that DeGiaxa (1) has shown that the polenta (mush) so largely eaten by the Italian and Roumanian peasant contains more water, and less proteids and fats than the composition of the grain would justify us in assuming, and that of the albumens actually present in the mush more than one-fourth (27.4%) are lost in the fæces: Neagoe regards the malady as resulting from the fact that those who develop it have lived for long periods of time alone on maize, which he regards as an insufficient food. That there is a connection between outbreaks of pellagra and scarcity of grain—as indicated by an increase of price—has long been known; Antonini (2) has recently again called attention to this matter. Quite recently, after more than a century of discussion, this theory has been rediscovered by Goldberger (1 and 2).

The foregoing is strong testimony in support of the belief that misery and insufficient food stand in an intimate connection with the causation of pellagra—at least these causes may determine the outbreak of the external symptoms—but that they can alone induce the disease seems highly improbable. When we compare pellagra with the clinical picture that is observed in starvation, such as is seen, for example, in carcinoma of the intestinal tract or in grave disorders of the digestive system, we find that they differ greatly. It may, however, be urged that the starvation of pellagra is of a much more chronic character, and that the disagreements in symptomatology may be due to this, but here again we are able to bring forward clinical evidence which hardly lends support to the view. It is well-known, for example, that the inhabitants of many parts of the world live in a state of misery, quite as great as that of the Italian and Roumanian farmer, and we likewise find in many countries the peasant class practically subsisting on one food, and yet it is only in those districts where maize is largely eaten that we see pellagra. The view might be advocated, and perhaps with truth, that individuals react to starvation in much the same way that they do to toxic substances, acquiring what might be called a sort of im-

munity in some cases, and that, furthermore, there may be invigorating influences in the countries free from pellagra that prevent the general occurrence of the malady; this might be allowed to a certain point with some degree of reason, but it is hardly conceivable that under such conditions we should only have an occasional case of parapellagra, which the records of medicine show to be exceedingly rare.

If pellagra be due to starvation we should naturally assume that it would be expressed in excessive hunger, but its records show that this is very rare,—its victims exhibiting almost always a marked degree of anorexia; this is even true in the intervals between the acute attacks.

Finally the matter would seem to be definitely settled by the now well-established fact that pellagra is exceedingly common all over the southern portion of the United States, and is daily observed among people in excellent circumstances who have eaten meats and all other necessary foods abundantly throughout their entire lives. To maintain, therefore, that pellagra is caused by inanition is to deny patent facts and to assert that which is obviously untrue.

We thus find that the greatest misery may occur over wide areas, as in China, India, Ireland and even other parts of Europe, without any record of pellagra having occurred, and on the other hand we see it every day in the well-to-do and even wealthy citizens of the United States who have eaten abundantly all their lives.

Finally we may ask if it be within the range of probability that chronic starvation could produce the lesions that we know always accompany pellagra, and if it could act in such a fashion as to reproduce the disease, with all of its symptoms and morbid alterations, in the offspring of its victims—even though they themselves might have been at all times well fed? He would be a bold man indeed who would answer in the affirmative. It seems, then, clear that however important the part may be that inanition plays in the causation of the clinical manifestations of this malady, there is some other element necessary for its production.

It is of interest to observe that some of the foremost writers on this subject have given this theory especial consideration, and have come to the conclusion that the facts will not bear out the view; thus we find that Dejeanne rejects the idea for the reasons already stated, as does also the very critical G. Strambio (Jr.); a similar opinion has been recently expressed in a very careful and able paper by Sandwith.

Since the foregoing was written, Goldberger and Wheeler have asserted that they have produced pellagra in the human being by subjecting them to a "restricted" diet for approximately nine months—the subjects being convicts who "kept about the same hours and did about the same kind and the same amount of work as the other convicts."

The volunteer squad upon whom these experiments were carried out consisted of twelve men in the beginning, but only eleven continued until the end, one having been released on account of the development of an intercurrent trouble. The experiments extended from February 1st and February 4th, 1915, to October 31st, 1915.

These authors give for the week ending August 8th, 1915, a specimen of the dietary employed. From this it is seen that the food consisted of biscuit, corn bread, grits, rice, fried mush, brown gravy, sweet potatoes, cabbage, collards, and cane syrup, each man consuming 3.32 pounds per day, which according to the experimenters, had a caloric value of 2,952. Leaving out of consideration the syrup, sugar and gravy, the author has calculated that each man consumed daily approximately 77.52 grams of protein, though it is, of course, true that not the entire amount was assimilable.

The "restriction" in these experiments appears to consist wholly in leaving out of the dietary animal food, though the total amount of protein is quite sufficient for maintaining nitrogen equilibrium, according to the best authorities of the present day.

Of the eleven volunteers who completed the experiment, he says:

"Not less than six developed symptoms, including a "typical" dermatitis justifying a diagnosis of pellagra. The nervous and gastrointestinal symptoms were mild but distinct. The dermatitis was first noted between September 12th and September 24th, 1915, or not later than five months after the beginning of the restricted diet. It is of great interest to note that in all of our cases the

skin lesions were first recognized on the scrotum. Later there appeared lesions on the backs of the hands in two cases, and the back of the neck in one case. The scrotal lesions conformed to the type described and figured by Merk. This experience would suggest that the scrotal lesion is a much more common early skin manifestation than has heretofore been believed. It would probably have escaped us, but for the fact that it was our routine to examine these men and the special control group completely stripped.''

Unfortunately the matter is far from being so simple, and the results obtained by these writers can not be regarded as unexceptionable.

In the first place it should be recalled that pellagra is certainly in many cases hereditary, and we have no evidence from the paper of these investigators that any inquiry was made into the ancestry of the persons employed for their experiments.

It is also unquestionably true that pellagrins probably always suffer for many years from mild symptoms before finally reaching that stage of the process when frank skin manifestations appear; if these authors have attempted to determine the antecedents of their patients in this particular, they failed to mention it.

Their reference to the fact that Merk, in his well-known work on the skin lesions of pellagra, makes mention of pellagraderms of the scrotum, is somewhat misleading, inasmuch as it would be assumed that this condition is common; on the other hand this writer only described and figured one case, which was that reported by Deiaco, and, if we except the few reported instances where the lesions were universal, is probably the only one in the literature of endemic pellagra. *

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*The author is fully aware of the cases of alleged pellagra reported two or three years ago by Stannus (Transactions Society of Tropical Medicine, 1913-14, pp. 32-56). This writer reported 131 cases of supposed pellagra from Nyasaland, but the recorded symptoms were of such a peculiar and bizarre nature in every way that there can be little or no doubt that they were not genuinely pellagrous. Among their many peculiarities we note the disease only occurs in the male; it comes on at any period of the year; no effort was made to determine the patients' histories, according to the report, and this writer, like many others, fails to recognize that typical pellagrous skin lesions pursue an extremely characteristic course; among the peculiar symptoms are that the skin lesions would appear to have begun around the elbows, followed by an erythema at the base of the thumb and inner two-thirds of the posterior surface of the hand, with no changes on the other fingers, in 49 of the 131 cases there was a lesion at the corners of the lips extending outward over the skin of the cheeks, and an erythema around the eyes, particularly at the internal and external canthi, lesions of the upper and outer portions of the ears, alterations of the prepuce, and inflammatory changes of the anterior and lower surface of the scrotum in 19 cases; there were occasionally slight changes in the gastrointestinal tract, but these were not marked; the same is true of the nervous system. He says:

''The rate of evolution of the rash is very variable; in some it is a matter only of days before many situations are involved, in others weeks or months; it may be evanescent, having disappeared entirely in a week or persisting for months, gradually fading and leaving for a much longer time a dark staining of the skin, best seen in the lighter skinned individuals. The same is true of the lips and tongue, affection of either or both of which may precede for some time the rash, and linger long after it has disappeared'' (p. 37).

Certainly there is little in the above to remind one of a typical pellagrous attack; its occurrence only in men, the apparent absence of early symptoms, the nature of the onset, the distribution of the rash and its duration and location, the mildness of the gastrointestinal manifestations, the lack of characteristic nervous symptoms, the frequent persistence of inflammatory changes in the mouth long after the skin rash has disappeared, and when we finally learn that the duration of the disease would appear to be from 5 to 25 months, the superficial resemblance to pellagra disappears, and forces us to the conclusion that the clinical phenomena are insufficient to warrant a diagnosis of this disease.

The like may be said of the one or two instances where scrotal lesions have been mentioned in connection with cases of pseudopellagra.

It is of particular importance to remember that in this case the lesions appeared in the usual situations before extending to the scrotum. In Goldberger and Wheeler's cases, however, we have a report of this very unusual symptom occurring simultaneously in one restricted group of individuals, and the lesions presumably only extended to other parts of the body in two instances! Certainly such an extraordinary occurrence in itself could hardly be described as "typical," and where this word is used by these authors it was probably intended to apply only to the character of the skin change. However, it would have been most desirable, in a matter of such transcendent importance, for full and complete particulars to have been given respecting the nature of these alterations; certainly the matter is of sufficient interest to demand the fullest description of the nature of the onset, the peculiar characteristics shown by the lesions, their course, and final termination. In this connection it should be mentioned that writers have been far too lax in their acceptance of various skin lesions as being pellagrous, a fact which is shown by the cases of Stannus just referred to, and by those reported as "pseudo-pellagra" or "pellagra of the insane," having not uncommonly been found on close examination to be nothing more than examples of parasitic skin diseases. Inasmuch as the typical lesions of pellagra follow a very definite and highly characteristic course, the value of these investigations would have been immensely increased had the report included such a description as would have made mistakes in diagnosis almost out of the question. It is furthermore to be deplored that we have no more definite data concerning the other symptoms than were given in the preceding quotation.

Irrespective of two cases where pellagrous lesions covered the entire body, the author has also seen at least one case of pellagrous scrotal erythema, and certainly if all other instances of the kind are accompanied by similar annoyance, there would be little probability of lesions of this kind "escaping" the clinician. Lying between the legs, subjected to constant friction and the heat of neighboring parts, the patient complained most bitterly of the inconvenience occasioned by this particular skin lesion, it, in fact, causing more distress than all the other symptoms combined. In view of this experience it seems rather singular that the cases referred to by Goldberger and Wheeler would have probably escaped observation but for their habit of stripping the patients for examination.

In conclusion attention should be in this connection directed to the fact that it has not been generally thought by those who have specially investigated the subject, that such a "restricted" diet as that employed by these writers in their investigations is of such character as to produce disease.

In the general summary of his latest book on this subject, our great physiologic chemist, Chittenden, says:

"It is quite evident from a study of the results obtained in the foregoing experiments that young, vigorous men of the type under observation, trained in athletics and accustomed to the doing of vigorous muscular work, can satisfy all the true physiological needs of their bodies and maintain their physical strength and vigor, as well as their capacity for mental work, with an amount of proteid food equal to one-half or one-third that ordinarily consumed by men of this stamp. As the results show, all these men reduced their rate of proteid metabolism in such degree that the amount of nitrogen excreted daily during the period of the experiment averaged 8.8 grams, implying a metabolism of about 55 grams of proteid matter per day."

It is also well-known that this distinguished investigator succeeded in maintaining in his own person nitrogenous equilibrium on from 37 to 40 grams of assimilable proteids daily.

In this connection it is also of extreme importance to note the fact that McCay has shown that the average Bengali assimilates on an average only 37.5 grams of proteid daily.

To much the same effect is the following from Oshima:

"The dietaries of the miscellaneous class (Japanese), including employees, prisoners, etc., consist largely of vegetable foods, but supply on an average 59 grams of proteid and 2,190 calories of energy per man per day" (p. 129).

It is thus seen that a reliable investigator has stated that a class of the Japanese live on a dietary notably less rich in protein, and almost two-thirds less in total caloric value than that employed in Goldberger and Wheeler's investigation. Furthermore it is so well-known that the peasants not only of Japan and China, but of many other parts of the world, so exclusively subsist on vegetable food that it seems hardly possible for serious investigators to suggest that food of this kind, even in insufficient quantity, could be responsible for so dreadful a disease as is pellagra.

In this connection the following quotation, again from Oshima, is interesting:

"The vital question, however, is not whether persons can keep well and strong upon a vegetable diet, for such is abundantly proven by practice and by experiment, but whether they can be equally as well or perhaps much better and more advantageously nourished on a mixed diet" (p. 130).

From the foregoing it would seem then that the only fault theoretically that could be found with this diet is that it was supplied in somewhat greater abundance than was actually necessary.

Finally, mention should be made of the fact that precisely one-third of the total food given the persons experimented upon consisted of maize products, and it is noteworthy that it is shown by the sample dietary that the subjects were given food of this kind at every meal, and in some instances in two different forms at the same meal. In view of the fact that foreign pellagrologists are almost a unit as to the relationship of maize to pellagra, and as it is held by some of the most eminent of them that the zein, and perhaps the ferments, contained in the normal cereal may be in a measure responsible for the production of the disease in question, and when we remember that practically all maize is more or less mouldy, and therefore contains phenol poisons, it seems most extraordinary that food of this character should have been allowed those upon whom these experiments were being carried out. Even if pellagra had been produced—which the author could not for a moment concede—it could and would have been claimed by foreign workers on this subject as being but a proof of the view for which practically all of them contend.

Theory of Toxins Produced by Fungous Growths (Moulds) in Maize.

As we have already seen the view that decomposing maize might have some relationship to pellagra was entertained by some of the earliest writers on this subject. Thus we find that Gherardini distinctly enunciates the idea, while Guerreschi puts forth this theory as an etiologic doctrine in 1814, and Bassi strongly advocates it in 1815. Subsequently it was elaborated by Balardini (1), and still later by Lombroso (2-11) and many others.

For the sake of clearness it will be necessary to consider the different phases of this subject under separate headings.

Investigations Which Demonstrate That Mouldy Maize Contains Poisons.

As we have already seen, along with the idea that pellagra is the consequence of the consumption of Indian corn, there developed almost simultaneously the view that this result is not wholly or indeed principally the consequence of any inherent bad properties maize

may possess, but that the malady is to be regarded as in the main the effect of noxious properties imparted to this cereal by the growth in it of various microörganisms, while still later it was suggested and subsequently proved that poisons are produced under these circumstances. In other words there has been a growing tendency among its students to look upon this affection as a sort of *ptomaine poisoning* of a mild but exceedingly chronic character, which they consider to be in every way comparable to those toxic states produced by eating more or less decomposed albuminous foods, or, still more accurately, to the pathologic changes that follow the continued consumption of bad wheaten products, or rye bread infected with the ergot parasite.

It is important to remember that no one has in recent years seriously regarded pellagra as being an infection conveyed through and by means of maize products, though suggestions of this kind have not been entirely wanting in the past. Thus we find that Majocchi (1) appears to have thought that his *Bacillus maydis,* which is found abundantly in Indian corn, might infect the human organism by being constantly eaten, and more recently Ceni (4-7) maintained that the moulds present in bad maize are taken into the body when this substance is ingested, and, later penetrating the tissues, produce pellagra.

We will now take up a discussion, as briefly as possible, of the various observations which have been advanced to show that pellagra is the result of poisons formed in fermenting maize.

That pellagra is not unlike some other toxic conditions in its symptomatology was early recognized by Strambio (4), who discussed its resemblances to ergotism.

Based on the clinical analogies between this affection and the disease known as *raphania.* Guerreschi somewhat later advanced the view that the former malady results from the consumption of mouldy maize—thus again evidencing an early recognition of the fact that pellagra bears a strong clinical resemblance to the intoxications.*

Of similar import is likewise the view, expressed by nearly all of the early investigators, that decomposing food and unripe and badly preserved maize have much to do with the production of this malady, but it was not until 1845 that this idea came into real prominence, as a result of the publication by Balardini (1) of his classical work

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*The reason that ergotism was formerly incorrectly called "raphania" was due to the fact that the affection was first described in Sweden in 1763, by the celebrated botanist, Linné, who was also a physician; the mistake was the result of the assumption that the disease is the consequence of eating the seeds of the *Raphanus raphanistrum,* which were supposed to become mixed with rye during harvesting. So great was the respect in which this remarkable man was held that the idea was persisted in long after it had been shown to be erroneous.

on this subject. The general theoretic considerations by which this writer was actuated have no part in the present discussion, it being only with his advocacy of the view that mouldy maize (verderame) produces pellagra that we are at present concerned. This writer thus describes this change in the seeds of Indian corn:

"This disease does not manifest itself until after the corn is ripened and is placed in warehouses. It appears in the oblong depressions covered by the cuticle of the grain, which corresponds to its germ. This cuticle—which in a natural condition is seen to be wrinkled and adherent to the embryo—is found on examination to be distended and somewhat turgid when it gives birth to this degeneration, and, though remaining for a time unbroken, shows beneath its surface a greenish material.

"On removing this mass one finds quickly that it consists of a green powder, with more or less of a tawny hue, and is found to be made up of the micro-parasite which first invades the substance of the grain in contact with the germ and ultimately destroys it; in many cases this part of the grain appears to be first injured, becoming then under such circumstances of a yellowish color, with spots here and there of an orange tint.

"On being mashed the morbific material referred to immediately separates into multitudes of fine globules, the smallest of which are recognized under the microscope as the spores of the germ. They are equal in size, perfectly round, transparent when either wet or dry, without internal structure, and on the outside smooth and most simple.

"A careful examination microscopically at once settles every question concerning their nature, for mixed in between them there are found filaments which are usually small; they are, it is true, rather rare, but their existence may be proved beyond question."

On the request of Balardini this material was examined by Baron Cesati, who did not hesitate to characterize these bodies as true parasitic fungi belonging to the genus *sporosorium,* and which this observer regarded as being new to science; they were called by him *Sporosorium maydis.*

Although sound maize appeared under the microscope to contain none of these parasites, Balardini truly remarks that it is extremely likely that it is never entirely free from them. He observes that they are most commonly seen after cold years and rainy autumns, which not only interfere with the maturing of the grain, but also prevent its being properly conserved. Balardini noted that this change was most common in warehouses used for storing maize, and where it was kept in humid places. This writer then goes on to give numerous instances in which pellagra developed to a much greater extent where persons had been known to eat mouldy grain for a considerable period of time than where this was not done.

Balardini, his son, and his assistant, experimented upon themselves with mouldy maize, and observed that it had a nauseating and bitter taste, and that on being swallowed it produced a sensation of

burning in the palate and fauces, extending down into the stomach; in addition there followed nausea, belching and malaise.

This investigator then made some experiments on chickens, and as the result came to the following conclusions:

(1) "That the nutritious portions of grain attacked by moulds are made less valuable as a nutriment, less able to repair the wastes in the body, and less strength-giving, causing in animals that eat it exclusively a slow loss of flesh and diminution in vitality—which appears to me to be the crucial test of its power to do harm.

(2) "This grain, when affected with verderame, contains a deleterious principle, acid and unassimilable, which exercises a noxious action upon the human organism, and can, if used for a long period of time, break down the organic union of the body, alter the normal condition of the digestive organs, and pervert the humors and other constituents of the blood, and finally induce a special pathologic state which is called pellagra; such changes are similar to those produced by the consumption of other cereals which have been acted upon by fungi, and which are known to produce peculiar states of disease in man."

Unfortunately knowledge of the hyphomycetes had not advanced sufficiently at the time Balardini wrote for him to identify with certainty the parasite which he found to be the cause of his "verderame," and we cannot therefore now be certain as to with what species of mould he was dealing—though that it was a mould, his description leaves no doubt. The name *Sporosorium maydis* has, therefore, passed out of use, and has for us now only historical interest.

Like Strambio and Guerreschi, Balardini did not fail to call attention to the close resemblance clinically between pellagra and ergotism. In this connection it is interesting to note that this writer says that in the new world there is a fungus, closely related to ergot, which affects growing maize, and which is known as *Sclerotium zeinum*. In Central America this fungus is called by the natives "peladero" and is thought by them to produce a curious infirmity called "pelatina," which causes the loss of the hair of the body, of the finger nails, and the teeth.

In the same year that Balardini's work was published, a most interesting monograph on this subject was written by Triberti, who agreed fully with the opinion of the former observer as to the causation of pellagra.

The views of Balardini for a time met with considerable opposition, by far the ablest and most important of his detractors being Morelli, Lussana and Frua, and later Gemma (6, 7), all of whom looked upon the malady as being frequently hereditary and always associated with inanition.

A few years later there arose, particularly in France, the memorable discussion relative to the possibility of certain forms of the malady having no connection with maize, it being claimed by Landouzy and Bouchard (1, 2) that the disease often develops sporadic-

ally, and by Billod (1, 2) that it frequently occurs among the insane—in both instances without the patients ever having eaten maize products. On the other hand the views of Balardini were warmly espoused by the Frenchman, Roussel, who, by the consummate ability with which he wrote, was largely responsible for the diffusion of a knowledge and that degree of acceptance of the maize theory which exist at the present day.

For a number of years following the publication of the writings referred to, nothing more was done of any importance in connection with this theory, its advocates and opponents settling down into two opposing camps, neither of which would grant to the other reason, justice or common sense, and neither deigning, as is the habit of those of a faith, to make such investigations as would tend to prove the truth of their respective views. So matters stood when the subject was attacked anew by the celebrated Cesare Lombroso (2), who, in 1869, began a series of papers in which he first advanced the theory that *toxines* are produced in maize by the growth of microörganisms, and further attempted to prove by the results of experiments that the maize theory of the causation of pellagra is justified.

This investigator used in his work both animals and men, his results with the latter being particularly curious. They will be referred to in the chapter on the physiologic action of mould poisons. It is noteworthy that this writer recognized the frequent presence of the *Penicillium* in bad maize, though he states that it is innocuous.

Lombroso (7) appears to have been the first to prove experimentally that poisons are produced in fermented wheat.

Balardini likewise contributed papers in 1872 and 1873, in which he recounted the result of further experiments on animals with mouldy maize. It is noteworthy that this observer particularly called attention at this time to the frequent presence of the *Penicillium* in bad maize, and appears to have been the first to suspect its connection with the poisons that the latter contains when mouldy.

In 1872 Lombroso and Dupré made a further step in advance in the study of this subject by their investigations respecting the chemical composition and poisonous substances of both sound and mouldy maize, and this was followed up four years later by Lombroso and Erba in a second article in which the conclusions arrived at in the first were extended and confirmed.

In the same year Lombroso (9 and 10) wrote a couple of articles in which he defended the work done by him and his collaborators.

Likewise in 1876 Pelloggio made a further contribution to this subject in an attempt to isolate alkaloids from mouldy maize. While he was not entirely successful, be obtained toxines that produced death when injected into frogs.

Somewhat later in the same year a paper on this subject was contributed by Brugnatelli and Zenoni, who operated with extracts presented them by Erba, and obtained a material which in some particulars resembled alkaloids.

In 1878 Husemann took up this subject, and in all essential particulars confirmed the previous work of Lombroso. This writer particularly called attention to a narcotic poison that acts first upon the brain and later on the spinal cord and medulla oblongata, and which, through paralysis of these organs, leads to death. It is noteworthy that the writer refers to the fact that this poison is mainly produced in the autumn and winter. He thinks there is perhaps another poison that produces tetanic contractions of the flexor muscles.

There is also, particularly in the warmer seasons, a poisonous substance that causes, when ingested, an increase in the reflexes and ultimately occasions a reflex tetanoid condition resembling that produced by strychnine; this toxine affects the peripheral nerves more markedly than does the narcotic poison, and, while much more powerful, like it, shows no direct influence upon the heart's action.

In 1880 Chiotto and Lussana wrote an interesting paper in connection with this phase of the subject. Chiotto, who did the chemical part of the work, confirmed the results of the investigators already mentioned in that he found alkaloidal bodies in decomposing maize, but the experiments on animals carried out by Lussana indicated that the substances obtained had little or no action, and the writers, therefore, came to the conclusion that they could not be the cause of pellagra.

The celebrated chemist, Hofmeister, of Prague, informed Neusser (1) that he had found two toxines in maize, one of which was soluble in alcohol and insoluble in water, and which had a paralyzing effect on animals, and the other, which was soluble in water and alcohol, gave alkaloidal reactions and produced in warm blooded animals a slightly narcotic effect, along with pronounced tonic and clonic spasms, resembling those occasioned by picrotoxine, though not being entirely identical with them; the poison cannot, however, be picrotoxine, as it differs from this substance chemically.

Monselise likewise investigated bad maize, but was unable to find any alkaloidal substances. He, however, states that they may possibly be formed in decomposing maize, but asserts that before the amount can be sufficiently great to produce symptoms the maize has acquired such an exceedingly disagreeable taste and odor that the hungriest man would refuse it.

The foregoing papers have dealt principally with substances that in the main were thought by their discoverers to be of an alkaloidal nature. That such bodies probably exist there can be little doubt, but the trend of subsequent investigators has been to seek for the pellagrous toxine in other chemical substances. Even during the time when the results of these investigations were being given to the world, the tendency referred to was evidenced by the appearance of a paper of a most unexpected character, considering its source.

The celebrated Selmi, discoverer of ptomaines, and one of the greatest investigators of these substances, published, in 1877, the results of his work on maize toxines, stating as his conclusion that

the principal poison is not of an alkaloidal nature at all, but that it in reality is *acrolein.*

As the result of the foregoing work Selmi was of the opinion that the maize poison is *ammonium acroleinate,* and that pellagra is the consequence of poisoning with this substance, either directly or by some of its decomposition products, such as *cyanides* or *nitrites.* As is the case with the theory that regards pellagra as being the result of poisonous alkaloids, further investigation has in no way confirmed the observations of Selmi, though no one had disproved them.

In addition it is highly interesting to observe that this distinguished investigator first suggested the possibility of toxic ferments being formed during the germination of maize, and showed by experiments that this actually occurs; the ferment—which has a powerful action on the component parts of this cereal—he names *zeastase.* Many years later Romaro (1, 2) assumed that this ferment is the cause of pellagra.

The next writer with views of any importance was Neusser (1), whose monograph appeared in 1887. In addition to valuable clinical additions to our knowledge of pellagra, Neusser advanced a hypothesis of maize intoxication that somewhat modified preëxisting opinions. While strongly believing that the malady is due to Indian corn, he proposed the theory that maize products when taken as food are in reality not toxic of themselves, but that some constituent of the cereal is the *mother substance of a poison* that is formed in the intestine. Under normal conditions, he thinks, this parent of the real toxine is digested or absorbed into the body without harmful results, while under other circumstances—particularly in persons inclined to dyspeptic disturbances—it goes on to the formation of poisons. As his reasons for this assumption the writer urges that persons often eat maize for years and then suddenly develop the disease, and that many individuals consume products of this cereal throughout life without suffering any ill consequences; in both cases he assumes that the digestion is in reality responsible for the immunity that is enjoyed. Instancing the often repeated example of poisoning from the toadstool, he makes, in the author's opinion, the natural and common error of demanding that the maize toxines also produce their effects as soon as taken.

The present writer is constrained to agree that the digestion plays an important part in the production of pellagra, it being a disease, at least in America, that is usually associated with persons of the dyspeptic type, and the patients almost always give a history of long-continued disturbances of the digestion. In explanation of this, however, it is not necessary to agree with the theory of Neusser, as the general weakening of the vital powers that results from disturbances of assimilation naturally lessens the capacity to resist disease-producing agencies of all kinds, whether they be of bacterial or chemical origin, and a predisposition to pellagra as well as other diseases would naturally follow. On the other hand, bodily strength is of the first importance in resisting pathogenic agencies, and nowhere is this

power more marked than where such influences belong to the group of intoxicants. No more striking example of this could be cited than the tremendous quantities of alcohol that young and vigorous individuals may habitually consume apparently without injury—quantities that would actually produce death in a few hours in others who are not so strong. It is, of course, likewise true that Neusser failed entirely to take into consideration the chronic but most pronounced alterations that are present in the bodies of those who have this disease, and which unquestionably precede by many years the outbreaks that are regarded as typical of pellagra. Neusser made no experiments to determine as to whether or not his view is correct.

As was seen in the chapter on the various microörganisms that have been supposed to stand in a causal relationship to pellagra, a bacterium was described in 1881 by the celebrated Italian dermatologist, Majocchi (1), which was supposed by him to produce pellraga as the result of infection. It was also noted that this germ was later found by Paltauf and Heider to be the potato bacillus, and it was definitely determined that it had no direct causal relationship to the malady in question. However, it was suggested that it might act indirectly by producing poisons in maize, and at the instance of Lombroso this matter was investigated in 1890 by Bordoni-Uffreduzzi and Ottolenghi. These writers showed that alcoholic extracts of cultures of this organism produced paralysis in white rats, and that after being allowed to grow on mush (polenta) for seven or eight days, the latter was found to be toxic when then fed to dogs. In view of these results the writers come to the conclusion that the potato bacillus does produce poisons in maize, but they are not of the opinion that they have any relationship to the production of pellagra.

A short time after the publication of the article just mentioned Lombroso and Ottolenghi gave to the world an account of experiments undertaken to determine whether the *Oidium lactis* produces toxines when grown on maize mush. The results indicate that a toxine is produced, as they found that alcoholic extracts injected into frogs, guinea pigs and rabbits quite constantly produced death in these animals—the lethal dose being in frogs 14 to 1,000 and in guinea pigs 18 to 1,000 by weight. Where death resulted it was accompanied by paralysis of sensation and motion.

In an exceedingly well written paper DiGiaxa (1), in 1892, considered among other things the etiology of pellagra. As the result of his experiments, which show that a large percentage of the albuminous constituents of maize pass through the intestinal tract undigested, the writer properly concludes that the number of bacteria must be greatly increased when this cereal is eaten and that, therefore, the quantity of the toxine in the intestinal tract must be much greater than normal. The same author (2) has likewise shown that when growing under such conditions the colon bacillus becomes particularly active and produces more virulent toxines than under ordinary circumstances. The writer then assumes that the toxic sub-

stances are increased in maize eaters, and that its habitual use for an indefinite period of time might well ultimately produce pellagra. It will be seen that this theory of DeGiaxa is essentially an amplification of that of Neusser.

Somewhat more accurate, but along the same general lines followed by previous investigators, are the observations of Monti, Tirelli and Pelizzi, whose writings appeared from 1890 to 1896.

The first of this series of papers was one by Monti and Tirelli, in which a number of different organisms obtained in maize were described; among these were the *Penicillium glaucum,* the *Mucor racemosus,* the *Rhizopus nigricans* (Ehrenberg), the *Sterigmatocystis nigra* (van Tieghem), the *Saccharomyces sphericus albus,* the *Bacillus subtilis,* and a number of *cocci,* among which are two liquefying organisms, one of which produces an orange and the other a white color.

In 1893-94 Tirelli (1) continued these observations and described a number of the organisms encountered. He records that he found a *mould,* the characteristics of which are described, and he then discusses the peculiarities of ten different bacteria. He describes an exceedingly small *diplo-bacillus,* attenuated at the ends, and with rounded extremities which produces transparent whitish growth in gelatine and agar: a second bacterium is likewise a *bacillus* somewhat larger than the preceding, with rounded extremities, developing rounded grayish colonies in gelatin, and a yellowish-lemon transparent, moist growth in agar: the third organism is likewise a *bacillus* that is three times as long as wide, and produces in gelatine a grayish growth, becoming in the deeper portions yellowish, and in agar a whitish growth that shows a greenish fluorescence: the fourth germ *resembles the preceding morphologically,* produces a grayish color in gelatine, with a greenish fluorescence, while in agar the colonies are raised, of a whitish-green color and fluorescent: the fifth bacterium is a *bacillus* larger in every way than the preceding, motile, and in gelatine produces colonies that are fluorescent, of an emerald green color, and show the same peculiarities in agar: the sixth organism is a *motile bacillus* that produces clear coral-like growths in gelatine, but this tint is gradually lost in old cultures: the seventh bacterium described was a *large coccus* that liquefies gelatin and develops a yellow lemon color in mush: the eighth germ was also a *coccus,* and produces in gelatin rounded, transparent, lemon colored growths: the ninth was a *large micrococcus,* and produces yellow, raised growths: the tenth bacterium is likewise a *coccus,* resembling in appearance the preceding, and develops in gelatin rounded cultures, with indented margins, and a watery appearance; in agar it shows metallic luster, but resembles in other particulars the organisms previously referred to. Of course the only significance attached to these organisms by Monti and Tirelli is that they assume that one or more of them may produce toxines while bringing about putrefactive changes in maize.

After examining many samples of maize Tirelli stated that where the seeds are dry they are never attacked by parasitic forms, and that where they appear to be sound are generally free from any great number of such organisms; where the maize is evidently bad, however, an enormous number of germs are found in it. He states that sometimes grains appear healthy without, but on investigation it will be found that many organisms have penetrated through the germ.

Tirelli admits that the number of germs described by no means represents the total bacterial flora of bad maize. He, however, thinks that the two fluorescent bacilli are of much importance, as they are rarely found except in bad maize. He notes that these germs, when growing in mush (polenta), lose their characteristic fluorescence and in fact produce practically no alteration in the appearance of this substance. The writer notes that *simply the boiling of mush is not sufficient to kill the germs that are encountered in bad maize.* He concludes by remarking that it is beyond question true that the poisons that together produce pellagra are in a considerable degree manufactured by the activities of the germs of putrefaction, which find a suitable medium for their development in maize.

In a subsequent paper Pelizzi and Tirelli together made a number of experiments on animals, using cultures in maize media of the various microörganisms discovered in bad Indian corn; these experiments showed conclusivtly that under proper conditions poisons are produced in this way.

In 1895 Tirelli (2) published another paper, in which he gave the result of numerous experiments confirmatory of those in the article just referred to. When poisons from bad maize are injected into dogs fever and pronounced psychic and nervous disturbances are produced, with a marked increase in the elimination of nitrogen compounds and of sulphides in the urine, and diminution in weight. As the result of his experiments the writer finally concludes that the poisons employed were capable of setting up pronounced disturbances of metabolism, and that a clinical picture is set up that bears a striking resemblance to pellagra.

In the same year there appeared an article by Carraroli (1), who described a bacillus which he had constantly found in bad maize, and which he thought produces in this cereal the toxines that cause pellagra. He states that the organism develops and is most active at the season of the year when pellagra occurs, and that it unquestionably elaborates a poison. It is likely that the writer was dealing with one of the organisms already described by Monti, Tirelli and Pelizzi.

From the foregoing it is evident that up to this time nothing had been done by investigators that could be said to have given any definite experimental basis for any one of the more or less conflicting views as to the method by which pellagra is produced from maize. The early experiments of Balardini and Lombroso were made simply with maize that was mouldy, though it is true that the for-

mer writer insisted that the poisonous principle was the result of the growth and development within the cereal of his *Sporosorium maydis;* when, however, later investigation clearly indicated that this organism was not described with sufficient clearness to enable mycologists to determine with just what parasite he was dealing, the results of his work were naturally greatly lessened in value. Some of the more recent writers, it is true, attempted to deal with definite organisms, but their results were of a too fragmentary character to be of any great significance. We may, therefore, say that with the publication in 1893 by Gosio (1) of an article dealing with the toxic substance elaborated by the *Penicillium glaucum,* a new epoch in the scientific study of pellagra was inaugurated—Gosio's work having the very great value that he dealt with a definite organism about the identity of which there can be no mistake, and that he has so ably continued his investigations with these and kindred moulds that the evidence which he has adduced, in the light of the literature of the past, is worthy of the most serious consideration of all students of the subject. These researches have also the added value that comes from confirmation, for many other investigators have followed in Gosio's footsteps, and have in a large measure corroborated and frequently added to the conclusions at which he arrived.

Gosio's first paper dealt exclusively with the *Penicillium glaucum.* He refers to the fact that previous observers had noted what undoubtedly was this organism, and had observed that the maize showing the greenish appearance which the growth of this germ produces was that which appeared to be associated with the production of pellagra. Previous writers, however, had not dealt with a pure culture of this mould, and their results can not, therefore, be accepted as conclusive.

Working with pure cultures of this organism grown on sterilized mush Gosio was able to determine that both water and ether extract from them aromatic compounds. These substances after purification by fractional crystallization are found to give phenol reactions—producing a color varying from blue to violet on the addition of solutions of ferric chloride, and also reacting to the Liebermann reagent; likewise they become fluorescent on the addition of resorcin and sulphuric acid. They are slightly soluble in cold water, very soluble in hot water, ether and alcohol.

This investigator is of the opinion that these phenol substances are the result of the diastatic action of the organism on the starches of maize. He calls attention to the fact that many hydrocarbons when fermented with the *Penicillium glaucum* furnish similar compounds—there occurring under such circumstances a true transformation from the fatty to the aromatic series of carbon compounds.

He feels certain that the phenol compounds must bear some relationship to pellagra, though the extent to which these substances may be inculpated depends naturally on their amount.

Gosio very properly concludes that it is perfectly certain that these moulds could *produce similar if not identical poisons when*

growing on other cereals, and that the rare cases of pellagra occurring in regions where maize is not eaten may be accounted for easily in this way. He points out, however, that this possibility in no way affects the great importance of maize as the determining factor in the production of pellagra—a fact that is clearly indicated by the extremely close association between the disease and the consumption of this cereal, and which is easily explicable when we remember, in contradistinction to other cereals, the great facility with which the physical peculiarities of this grain permit the invasion of micro-organisms.

In 1896 Gosio (2) wrote a second paper, in which the foregoing results are confirmed. In this article he particularly refers to the fact that the most frequent alteration in maize is produced by the *Penicillium galucum,* and he demonstrates that different cultures of this organism vary in their capacity to produce toxines; cultures that show little or no activity may be rendered more virulent by placing them in appropriate surroundings, particularly as regards temperature.

In the same year Gosio and Ferrati published further experiments with the toxines found in bad maize, showing that they are probably phenol acids. They found that repeated injections increase susceptibility.

This paper was shortly followed by an article by Pelizzi, in which he confirms the previous work of Gosio respecting the mould toxines.

In 1899 a paper on the action of moulds on maize was published by Antonini (1), this writer confirming in every particular the results of Gosio as regards the presence of the poison, and the close relationship that it bears to phenols.

He also noted the fact that while the acidity of maize increases along with the augmentation in its deterioration, this occurs only up to the point where decomposition begins to be pronounced in the albuminous parts of the grain, at which time the *ammonia produced neutralizes the acids previously formed* from the starchy substances. This is a matter upon which too much stress cannot be laid, as it clearly points out the source of possible error in testing for deterioration of maize by estimating the acidity. In instances where the albuminous decomposition is extreme the meal may even show an alkaline reaction.

In the following year Ferrati (1) made a further contribution to this subject, showing that extracts of maize meal fermented with the *Penicillium glaucum* are poisonous to dogs when administered by the mouth. It is of interest to note that this writer makes mention of the fact that the *moulds* frequently induce a high degree of change in maize without causing alterations such as would make the grain, when ground, obnoxious to sight, taste or smell—in this particular differing from the *bacteria* that produce forms of decomposition which are often exceedingly offensive.

In 1902 Gosio (3) presented a most interesting and thoughtful paper to the Second Italian Pellagra Congress, in which he reiter-

ated the conclusions at which he and the investigators previously named had arrived. This writer, after what one must admit to have been a cautious and conservative statement of the facts up to that time adduced, affirmed that in his opinion these facts warranted the conclusion that there is every probability that pellagra is the result of toxines elaborated by different species of the *penicilli.*

In discussing the paper just referred to DiPietro refers to the fact that he has himself gone into the subject of the bacteriology of maize very carefully, and has come to the following conclusions:

He has never found the *schizomycetes* in sufficient number in bad maize to warrant the view that they are of importance in the etiology of pellagra; he, therefore, felt justified in throwing them out of consideration. The same was true of the *streptothrix* and the *blastomycetes,* the former being very rare in bad maize, and no single species of the latter being known to produce toxic substances. He, therefore, turned to the *hyphomycetes* to find in the members of this group the active agents in the production of the pellagra toxine. He thought there could be no doubt that we should find in the *aspergilli, penicilli* and *bothrites,* either singly or together, the real pellagra-producing agencies.

In a number of investigations he was able to determine only that the *Penicillium glaucum* produces poisons—the toxine appearing on the third day, being augmented on the fifth, and reaching its greatest amount on the fifteenth day following planting, after which it remains constant.

It is interesting to note that DiPietro considered himself to have demonstrated some connection between this poison and pellagra in the following way: he injected into a guinea pig 8 c. c. of serum from a cured pellagrin, and after 14 hours he followed this by introducing 1 c. c. of the poison of the *penicillium*—at the same time injecting a control animal; in the one receiving the serum no ill effects followed, while in the latter the characteristic poisoning resulted. During the same year this author published in a separate paper (1), and in a much more elaborate form, the results that have just been referred to.

In the discussion following the reading of Gosio's paper, to which reference has just been made, it is interesting to note that Ceni stated that the heart, lungs, pleura and meninges of those dead of pellagra showed evidence of infection by aspergilli; he further affirms that such infections are usually associated with the consumption of maize, this observer believing that there is a connection between the two.

The next papers of importance appearing on this subject were articles by DiPietro (2-6), appearing in 1902-3-4, in which he discussed at considerable length the chemical peculiarities of toxines produced by the *Penicillium glaucum.* He has devised a modification of Gosio's test for the phenol toxines of moulds.

DiPietro asserts that this reaction is never given by sound maize, and is only obtained after this cereal has been acted upon by moulds.

During the years 1902 to 1910, inclusive, a large number of articles were written on moulds by Ceni (2-26), the greater part of them alone, but in some cases in collaboration with Besta (1-6), and once with Costa; several papers likewise appeared by Besta (2-5) alone. Notwithstanding the extraordinarily voluminous character of these articles—which together comprise many hundreds of pages—the actual facts demonstrated are but few.

Much of the subject-matter of the papers referred to was taken up in the attempt to prove that there is a variation in the toxicity of moulds entirely dependent on the season of the year. Credit for this conception is generally given Ceni and his collaborators, but as a matter of fact the observation was first made by Husemann, who not only showed that the toxines produced by moulds differ greatly in winter and summer, but also distinctly stated that the poison of the winter is of a depressant character, and that that produced mainly in the summer has the opposite effect. He also states that there is perhaps another poison that resembles nicotine in its action on the flexor muscles.

Notwithstanding that Ceni's experiments clearly lack unity, and that they were made under most varying conditions of temperature and culture media, he has steadfastly insisted that these important influences were in no way responsible for the results obtained, obstinately adhering to his opinion, despite the clear proof to the contrary adduced by Gosio (7), Palladino (2,3) and others. Ceni (8), and Ceni and Besta (1), and Besta (5) have also continued to maintain that the toxic principle produced by moulds resides in the spores.

Gosio (2) appears to have discovered the important fact that not all of the varieties of the *Penicillium glaucum* are toxic; more recently the subject has been investigated by DiPietro (2) and by Ceni (21, 22). Ceni and Costa also showed that the *Aspergillus fumigatus* and *Aspergillus varians* produce toxines; the poisonous substances were obtained by extracting the mould cultures with alcohol and afterwards evaporating; they state that these poisons resist boiling for at least 15 or 20 minutes. In a subsequent paper the former writer (11, 13) claimed that these organisms are dependent on season for the character of their toxines, and somewhat later (12, 15, 16, 17) stated that different strains of the *penicilli* vary in the character of the poisons produced as a result of like influences. Subsequently (13) this observer wrote an article on what he called a new *species* of *Aspergillus varians* which produced toxines; the writer probably meant *variety* instead of *species*. In another article (14) he maintains that the toxine of *Aspergillus ochraceus* is not produced to any extent at all in the winter, and still later (19) asserts that the penicilli produce phenol compounds very inconstantly. Subsequently (20) he describes a mould which he regards as new, giving it the name of *Aspergillus bruno gigante*, which he says produces poisons mostly in the spring and autumn. One of the most interesting of this writer's papers (21) is that which followed during the

same year, in which he shows that a number of moulds, that had been tested in Germany and found to be entirely free of toxines, produced poisons after being brought to Italy; unfortunately no data were given that clearly show whether this was simply an effect of climate, or a result of difference of temperature and culture media. In another article (22) he says that the penicilli in cheese are poisonous to dogs. In still another communication (23) in the following year he confirms Gosio's experiments showing that moulds when grown on wheat produce poisons resembling those elaborated by these organisms in maize; the writer maintains that these also are seasonal in their occurrence. In a still later article (26), which appeared in 1910, Ceni made some interesting observations, in the main confirmatory of previous investigations by Gosio, on the effect of light rays on moulds. He showed that direct light, independent of its heat rays, impedes the development of *Penicillium glaucum*, alters its chromogenic power, and to an even greater degree inhibits the elaboration of its specific poison. By allowing the light to pass through different colored glasses he determined that the violet and green rays are those that exercised the greatest influence. He also found that the various peculiarities of the germ were not affected to the same degree by the different rays; for example, the violet rays inhibit the development of a mould, but do not modify its chromogenic powers, or impede the production of poison; on the other hand the red rays exercise no influence on the development of the germ or its chromogenic power, but diminishes the elaboration of poisons. In a number of other articles, some of a polemic character, he defends his thesis respecting the influence of season on the development of mould poisons, and is very bitter in the denunciation of some of those who have objected to his views. It is noteworthy, however, that in one of his papers (22) that appeared in 1907, he admits that the influence of season is not invariable.

His collaborator, Besta (1, 2), has written two articles on mould toxins independently, in one of which he maintains that the toxine obtained by Ceni and himself differs from that of Gosio, and in another he asserts that the poison resides both in the *spores* and in the *mycelii* of the moulds—though the quantity is much greater in the former. He likewise says that the poison has nothing to do with the phenol bodies described by Gosio and DiPietro.

Tiraboschi (1) has recently written a most careful and valuable article on the various moulds that infest maize in stowage.

Character and Physical and Chemical Peculiarities of the Toxines Produced in Maize by the Growth of Various Microörganisms.

Unfortunately our knowledge of the chemistry of mould toxines is far from complete, there having been so far isolated only a few of the substances that result from the life activities of these organisms; as respects those elaborated in maize by other low vegetable forms we are virtually in complete ignorance. It is furthermore true that not all of these bodies have been shown to be toxic to ani-

mals, but inasmuch as their final status has not been settled, they may be, for convenience sake, considered along with the compounds that are known to be poisonous.

While Balardini showed in his classical treatise on the causation of pellagra that mouldy maize is toxic, he made no definite attempt to explain the fact, nor did the earlier investigations of Lombroso aid us materially in this particular—this observer only having determined, in 1870, that there are toxic substances produced in maize which are soluble in alcohol, and that they resist the boiling temperature, and are not destroyed by the heat usually employed in baking.

The study of the chemistry of the poisons of decomposing maize received a new impetus in 1872 as the result of the publication of a paper by Lombroso and Dupré, who announced that they had obtained from artificially fermented maize a series of substances that were shown to have decided toxic properties; they likewise investigated unfermented maize, with the idea of determining as to whether or not the extract from this substance differed in any way from that obtained from the decomposing cereal.

It was first observed that when good and bad maize are placed in 90% alcohol the latter gradually assumes a reddish color, and this is accompanied by a similar change in the tint in the alcohol; on the other hand no alteration is observed where good maize is used, though the alcohol takes on a rather faint, lemon-yellow color.

It was observed that caustic potash produces a red coloration, with the evolution of a distinct odor of bad maize when the residue that remains after evaporating the extract is washed with ether, to remove fatty material, and is later treated with this reagent. A more or less similar color is produced by caustic potash when added directly to the bad maize, though the tint is of a darker color, with a tendency to brown; where such a mixture is neutralized with sulphuric or tartaric acid a coffee colored precipitate occurs, with a distinct musty maize odor.

In the investigation carried on by these observers the maize, as before stated, was artificially fermented; it was placed in a large covered cask, and water added until it was at least two centimetres above the solid material, and the whole set aside in a warm place; every day the mixture was thoroughly stirred. As a consequence of the action of various organisms, it was evident that acetic fermentation was produced, and that later alcohol and lactic acid were elaborated. Finally, after the maize became putrid, the solid content was taken out and dried.

Examination at this time showed the presence of *A. glaucus, Oidium lactis, Rhizopodum nigricans, Eurotium herb.*, and many *vibrios.*

When the fermentation occurred in summer the maize was simply dried in the sun, while in the cooler seasons of the year evaporation was aided by placing the material in a drying oven until there was a loss of at least 24% by weight. After drying the maize was ground into fine meal, and preserved in 40% alcohol—this forming the tinc-

ture employed by Lombroso and Dupré, and Lombroso and Erba in their various investigations.

When the tincture just referred to is distilled on the water bath there remain three substances:

(1) The first of these is liquid at ordinary temperatures, is red, extremely acrid and bitter, and has a pronounced odor of bad maize; it is soluble in alcohol and ether, insoluble in water, upon which it floats, is neutral to litmus, becomes resinous in the air, and does not give precipitates with iodine in iodide of potash, with bichloride of platinum, or other metallic salts; it gives a clear yellow precipitate with solutions of potash and with benzine; from the foregoing it was thought that this is the oily part of maize, modified, and colored red by a substance which may be separated from ethereal solutions with caustic potash. This product, for brevity's sake, was called *the oil of bad maize.*

(2) The second substance also has a reddish brown color and viscid consistency, exhibits a pronounced odor of bad maize, and has a nauseating, bitter taste; it is neutral to litmus, soluble in dilute but insoluble in pure alcohol, which causes a precipitate in the form of yellow flakes, and insoluble in ether; with a solution of iodine and diodide of potash it gives a flocculent precipitate, which easily separates when a little dilute sulphuric acid is added; a yellow precipitate is produced by bichloride of platinum, and a green precipitate with sulphate of copper, which quickly changes into oxide; it is soluble in glacial acetic acid and in caustic potash, from which it may be precipitated with sulphuric acid; when treated with excess of water it separates into two parts, the one insoluble, which settles to the bottom as an amorphous brown powder, and another which dissolves with the production of a clear yellow color. This material was called, for brevity's sake, *the toxic substance of maize.*

(3) The third substance coagulates as the result of the action of ether, becomes very hard if it remains in contact with the air, is insoluble in alcohol, in solutions of potash, in water, in absolute alcohol, and in benzine; it softens from heat, and may be drawn out like wax; it burns with a white flame, giving off the odor of burnt mush. This material was called *the glutinous substance of maize.*

Good maize treated in a similar way likewise yields three substances: one of these is soluble in ether, with the production of an amber-yellow color in place of the red tint, and does not present the acrid odor of the red material of bad maize. It is not precipitated by benzine, and has indeed the properties of common maize oil; it does not become resinous on exposure to the air: another of these substances, likewise yellow, does not give a flocculent precipitate with absolute alcohol, but with a solution of iodine and iodide of potash, while with caustic potash and sulphuric acid a liquid (sic) precipitate occurs which is soluble in ether: the third substance is in every way like that which has been called the glutinous substance of maize, already referred to.

The difference between the materials obtained from good and bad maize is that from the former a yellow oil is extracted, which does not become resinous, while from the latter an oily product is obtained which is red in color, and of an acrid bitter taste, and which becomes resinous in the air; furthermore bad maize gives a reddish material, with reactions resembling those of alkaloids, such as are obtained with iodine and bichloride of platinum, etc.—a result which does not occur with the materials obtained from the normal product.

These writers particularly call attention to the close resemblance between the extract obtained from bad maize and that which may be got from ergot; it is further true that both are poisonous, though the toxic symptoms produced by the former are of a mild character.

In the same year these results were confirmed by Arnauld.

Four years later Lombroso and Erba reported to the Royal Institute of Lombardy the results of further work on this subject. Operating in the same manner as was done by Lombroso and Dupré, these writers obtained the three substances already considered and which were described by the latter investigators.

Lombroso and Erba have changed the nomenclature of these substances as follows:

(1) The oily substance is called *oleoresin.*

(2) The extractive material, resembling ergotin, soluble in water in all proportions, and in dilute alcohol, but insoluble in pure alcohol, is called *pellagrozeina.*

(3) The resinous substance, which softens but does not dissolve in boiling water, which carbonizes with sulphuric acid, and which is insoluble in hydrocarbons, but dissolves in caustic alkalies, is called the *resinous substance of maize.*

These investigators likewise speak of a fourth substance which they obtained from the residue left after the treatment with alcohol, which on account of being soluble in water is called by them the *aqueous extract of bad maize.*

It is noteworthy that these writers observed that the character of the fermentative change in bad maize shows seasonal variations; for example, they pointed out that the oil of bad maize is intensely bitter, has a chocolate color, and a pronounced odor when the putrefactive change has occurred in July and August, while that obtained in September is of a lighter tint, and not so bitter. They also obtained a similar oil from "pane giallo" (yellow bread).

At the same sitting of the Royal Institute of Lombardy, when the paper just referred to was presented, Pelloggio likewise made a further contribution to this subject. This writer attempted to obtain a purer and more concentrated product than had been secured by previous investigators, but he was not able to isolate any distinct and separate substance, though he obtained extractive material that produced death in frogs.

He proceeded as follows:

After having made an alcoholic extract of bad maize, this was diluted, and to it was added a solution of neutral acetate of lead

as long as a precipitate occurred; the precipitate was then filtered off and basic acetate of lead added in the same way, followed by a second filtration. Through the filtrate hydrogen sulphide was passed in order to remove any traces of lead that might remain after filtration, and the filtrate concentrated on the water bath to two-thirds of its volume; while still hot it was again filtered and further concentrated to one-tenth of the original volume. On cooling, no crystalline precipitate occurred. The liquid was then treated by the method of Stas. The ethereal extract was evaporated at a temperature of from 20° to 25° C. (68°-77° F.), and there remained a yellowish substance that floated on water, and a turbid liquid similar to that obtained from the organs of animals; the latter had an alkaline reaction. The liquid was then dried out in the desiccating apparatus of Fresenius at ordinary temperatures, but there was no crystalline solid remaining. The solid residue was taken up with water, slightly acidulated with sulphuric acid, and the solution again evaporated in the way just indicated, and there remained a yellow substance partially amorphous and partially crystallizable—the latter probably being sulphate of soda. This mass was treated repeatedly with ether, which, on evaporation, left a material that resembled alkaloids. With bicarbonate of soda and phosphomolybdic acid it gave a white precipitate, while with a solution of iodic acid there occurred a yellow precipitate; picric acid also gave a yellow precipitate. With tannin there was a brown precipitate, with iodine and iodide of potash an orange precipitate, with an aqueous solution of iodine and mercuric chloride there was a yellowish precipitate; with trichloride of gold there was a white precipitate, and with iodide of gold dissolved in iodide of potassium there was a brown precipitate.

The writer is uncertain whether the substance was a glucoside or a basic amide. He says it was the first time that a substance which acts like an alkaloid has been obtained from one of the vegetables ordinarily used for food.

Somewhat later in the same year a paper was also written on this subject by Brugnatelli and Zenoni (1), who operated with extracts presented them by Erba.

Employing the Stas-Otto method, they obtained a solid material, insoluble in water and non-crystallizable, which reacted as an alkali to litmus, and which was never entirely purified. This material behaved like strychnine in its color reactions, though the tint is more persistent; the blue color changes only after some hours into a grayish green. The substance is very bitter, but not so much so as strychnine.

These writers also operated with an extract which they obtained from thirty kilograms of maize bread and isolated a substance that was bitter, alkaline in reaction, and that contained nitrogen. In the state of an acetate or tartrate it gave precipitates with all of the reagents for alkaloids. This substance and its salts dissolve in sul-

phuric acid, with the production of an intense blue color on the addition of oxidizing agents.

In the same year Lombroso (8,9) wrote a couple of articles, in which he defended the work done by himself and Dupré and Erba, and particularly took issue with Brugnatelli as respects the latter investigator's suspicion that the material given him by Erba contained strychnine. Lombroso asserts that the great chemist, Berthelot, likewise examined some of the same material sent to Brugnatelli, and that while the former obtained a strychnine-like substance, it was found that is was not crystallizable, and that it did not give rise to chinolin on the addition of potassium hydrate. It was further observed by Lombroso that pure strychnine is insoluble in absolute alcohol and in ether, and little soluble in oil, while the body obtained by Brugnatelli did not present these characteristics, and he therefore assumes that this substance could not have been strychnine.

New interest was added to the chemistry of bad maize in the following year by the publication of a paper on this subject by Selmi, the discoverer of ptomaines.

This investigator treated mouldy maize with carbon disulphide, evaporated the extract, and saponified the residue with sodium hydrooxide, from which the poison *acrolein* (Allylaldehyde, C_3H_4O) was extracted with boiling alcohol. This alcoholic solution of acrolein is concentrated in vacuum, and taken up with ether, and then treated with alcohol, to which ammonia had been added, and from the mixture he obtained an amorphous precipitate of *ammonium acroleinate.* The alcohol concentrate likewise contained a resinous mass insoluble in carbon disulphide; but which dissolved in caustic alkalies, with the elaboration of ammonia.

Inasmuch as the extract of bad maize has been shown to contain acrolein and ammonia, Selmi suggests the possibility of the two existing in combination in maize products under ordinary conditions, and that pellagra may, therefore, be an intoxication which is the result of *ammonium acroleinate.* This writer also discusses the possibility of the substance just mentioned decomposing, with the production of either nitrites or cyanides, and, as both are poisonous, the clinical phenomena of pellagra might likewise be induced by these substances.

In 1878 Husemann likewise investigated this subject and clearly differentiated at least two poisons, and possibly a third, though he did not succeed in obtaining them in a pure state. He considered them as being of an *alkaloidal nature.* Nothing was found that acted like picrotoxine. In this year a second article on the same subject was published by Brugnatelli and Zenoni (2).

In his most excellent brochure on pellagra, Neusser (1), in 1887, mentioned that he had been told by Hofmeister that he had found in bad maize, which had not been artificially fermented, *two toxic substances,* one of which was soluble in alcohol but insoluble in water, while the other dissolved in both of these substances. The chemical

peculiarities of these substances were such that there could be no possibility of their being *picrotoxine.*

Since the earliest publications on this subject no paper has appeared which is more interesting or suggestive than that of Neusser, to which reference has just been made. Believing that there could be no question of the fact that maize is ordinarily in some way responsible for pellagra, this writer conceived the possibility of this cereal's containing a mother-substance, which, when taken into the intestinal tract, undergoes chemical alteration in some persons, and as the result of which poisons are formed which produce the symptoms of this malady. The individuals who have this predisposition are probably those whose stomach-digestion is weak, allowing the parent compound of the poison to pass through without the usual alteration. As an example of this possibility he quotes the investigations of Widtmann and Denk, who observed that certain individuals may take for years amygdalin without harm—never suffering any ill consequences so long as this substance is destroyed before reaching the intestines, but producing poisonous effects should it do so. Some animals, like the cat, whose intestines contain no amygdalin splitting ferments, are constitutionally immune to this poison, while the herbivorous animals, like the rabbit, are very susceptible to it.

After formulating the foregoing theory, Neusser discusses the various possibilities as regards the chemical changes that may occur in the intestine, mentioning that a harmless mother-substance may be converted into poisons by oxidation, splitting, reduction, hydration, and methylating—the two first mentioned being the changes that are most likely to occur. By these changes it would be possible for Selmi's ammonium acroleinate, by a process of oxidation and hydration, to be converted into *nitrites,* which are much more intensely toxic than this substance itself. It is likewise possible that the analine isomer *picolin* (C_6H_7N) might be formed.

It is further observed by Neusser that while amygdalin has never been found in maize, it is quite possible that some related *glucoside* may be present which under the action of acids may be split up in the intestinal tract into sugar and poisons. It is suggested that the contradictions in results of the researches by different writers concerning poisonous effects of maize products may be accounted for on the theory that in some cases the investigator may have been using a glucoside, while in others the substances resulted from the decomposition of such bodies, either one or the other being toxic, as the case might be.

Neusser then discusses the much mooted question of pellagra and pseudo-pellagra, and tries to reconcile the opposing views in the following manner: He directs attention to the fact that many writers have laid great stress on the causal relationship of the habitual use of alcohol and pellagra, it being in Spain even at the present time the commonly accepted view as to the etiology of this malady. This observer conceived the idea that some substance might be carried over in the alcoholic distillates which might either directly or in-

directly act as a poison. As an example of this possibility he mentions that in the manufacture of spirits from potatoes a poisonous principle found even in good potatoes, called *solanin*, may be often found in the distillate—a much greater portion of this toxine being produced where the potatoes are sprouting or decayed, in which conditions they are frequently employed. Following out this idea he had distillates prepared from two samples of bad maize; as they were both of an acid reaction, he added to one of them caustic potash, with the idea of liberating from their salts any possible volatile alkaloids that might be present. Both samples were then redistilled. The distillate from the unneutralized liquid, after being rectified, was found to be acid, and gave with acetate of lead an abundant precipitate, reduced copper oxide and ammoniacal silver solutions; the iron chloride reaction for volatile amids and the reaction for prussic acid were negative, as were the tests with brucin and with diphenylamin for nitro-glycerin. On the other hand there was a characteristic reaction for *aldehyde* with rosanalin and sulphuric acid. *This distillate was intensely poisonous.*

Alcoholic beverages of maize origin may thus, he thinks, cause pellagra without the victim ever having eaten this cereal.

The distillate from the maize rendered alkaline was found after purification to be neutral in reaction and to be *free from ptomaines, and was harmless when injected into animals.*

Following Selmi, this writer observes that since it is well-known that some poisonous alkaloids are destroyed by heating with alkalies, this may explain the apparent immunity from pellagra of the Indians of the new world, who, while living on maize regularly, use ashes, soda or lime in preparing their bread.

As regards the possibility of pellagra resulting from the consumption of alcoholic drinks made from maize, the writer again calls attention to the presence of aldehyde in the distillates employed by him, and remarks that this substance may of itself be poisonous, or might in the body be easily converted into some toxic derivative. He mentions that Kakule has observed that *croton aldehyde* is the first condensation product of the aldehyde group, and it is suggested on account of the near relationship that *collodins* might be formed; as the collodin and hydrocollodin ptomaines are very poisonous, this idea might be profitably followed up. It is also possible that poisons could result from the decomposition of aldehyde resins and of the glucosides—the latter supposition being quite in keeping with the theory already advanced in connection with these chemical substances. Neusser thinks it strongly probable that the pellagrous poison passes over in the distillate when whiskey is made from mouldy maize.

In 1880 Lussana and Chiotto likewise demonstrated poisons in fermenting maize, but were strongly disposed to deny their pellagrogenic power.

The theoretic possibility suggested by Neusser that the principal poison produced by moulds in maize media might be a *glucoside,* appears to have occurred to DiPietro (1, 3) some fifteen years later,

and this observer made a number of investigations with this idea in view. After a careful investigation he determined that the *Schizomycetes* are ordinarily never in sufficient quantities in bad maize to be of any importance, and the like is true of the *Streptothrix;* he likewise was of the opinion that the *Blastomycetes* were equally incapable of producing pellagra, as no single species of this genus is known to elaborate toxines; he, therefore, turned to the *Hyphomycetes* and determined that the only species of this group that possesses marked toxic properties when taken by the mouth is the *Penicillium glaucum.* As before stated, his investigations early connected themselves with the idea that the pellagrous toxine is probably a glucoside, and he endeavored chemically to show the truth of this view. He found that the poison, which appeared to reside altogether in the spores, resists boiling water, but decomposes when boiled in a solution of acids. DiPietro's idea was that the glucoside occurs as the result of a chemical union, in which an aromatic acid, manufactured from starches, plays a dominant rôle. He believes that this acid likewise occurs in the culture medium as a salt, it being united to some unrecognized base; it is likewise the case, he thinks, that it also occurs to a small extent in a free state. He determined that in the last named condition it reacts with ferric chloride, with the production of a green color, but produces no change when added to either of the two substances first referred to; however, the salt may be decomposed by the addition of some stronger acid, and the glucoside may be decomposed with the liberation of the aromatic substance referred to, after which the green coloration with ferric chloride may be easily obtained. These considerations are of some practical importance in testing maize for the presence of moulds, the true amount of change produced in them not being evident until the compounds just referred to are decomposed by acids and boiling, followed by the ferric chloride test.

The toxic principle, though never obtained in a pure state, was found by this investigator to be soluble in alcohol, chloroform, ether, fats and petroleum, but less so in water. It gives no precipitate with acetate of lead, and a very soluble salt is formed when an alkaline hydroxide is added to a solution of the acid.

Notwithstanding the interesting and somewhat important conclusions arrived at by DiPietro, it is not by any means certain that he is correct in the view that the principal toxine produced by moulds is a glucoside, though that it is possible has been admitted by Gosio, who is by far the greatest worker who has yet written on this subject; Alsberg and Black are inclined to disagree with DiPietro.

Following out the principles just enunciated, the test of Gosio was modified by this investigator—the new procedure being based upon the observation that the ferric chloride reaction is very greatly strengthened if the culture be previously acidified, and particularly if it be still later boiled.

A description of the technic of the test will be found on page 349.

By far the most important investigations which have been car-

ried out on moulds and their toxines were those of Gosio (1-9), he having written a number of illuminating papers from 1893 up to the present time. This observer first directed attention strongly to the moulds as the probable source of the pellagra toxine, and he was likewise the first to employ in this connection pure cultures—or what were thought to be such.

In his first paper Gosio (1), using the *Penicillium glaucum*, arrived at the conclusion that this organism decomposes hydrocarbons of all sorts, with the production, probably through the medium of ferments, of a series of aromatic substances, some of which are toxic. He observed that the most striking chemical peculiarity of cultures showing toxicity is the formation of an intensely blue color on the addition of solutions of ferric chloride, and it was later found by him that this reaction is very general in mould culture media which showed toxicity. This reaction is believed by the writer to indicate the presence of phenol compounds, though its exact significance is open to some doubt. Apparently unknown to Gosio, Raulin noticed when experimenting with cultures of *Aspergillus niger* many years before that in the absence of iron these organisms produce a substance that gives a red coloration with ferric chloride, and it was thought by this observer to be the consequence of the formation of a sulpho-cyanide. More recently Javillier and Sauton confirmed this observation, though their interpretation was different. They showed that the reaction fails when the organism is grown in the absence of both iron and zinc. Raciborski has likewise obtained a similar reaction with a number of fungi, and concludes, with Gosio, that this result is due to the formation by the hyphomycetes of a variety of aromatic substances.

The physical and chemical peculiarities of these phenol compounds, according to Gosio, are the following:

After the green penicillium is allowed to grow on maize mush the chemical products of its metabolism may be removed by extraction with ether. If the ether then be slowly evaporated we find that there remains a brown oil, that congeals on the surface; beneath is an aqueous residue containing the poisons mentioned, which gives with ferric chloride the violaceous color already referred to, and which likewise assumes a fluorescent appearance on the addition of an alkali. Being highly volatile it is possible by fractional distillation to purify these phenols; they are acid, and they give the Liebermann reaction; on the addition of sulphuric acid and resorcin a fluorescence is obtained. They are slightly soluble in cold water, though easily dissolved in ether, alcohol and hot water. Their alkaline salts, and those produced by the action of alkaline earths are soluble in water. They were likewise found to be antiseptic. In a later paper the writer says that the toxine or toxines are precipitated by dilute basic alkalies, but are soluble in acid alcohol.

About the period of sporification a number of substances of pleasant odor are liberated when the culture is treated with alkalies, with the production of vivid colors that disappear on addition of an acid,

but reappear on treatment with basic substances. These bodies are easily extractable with ether in the presence of phosphoric acid, and are even more soluble in acetone.

Early in the course of his work Gosio determined in mould cultures an aromatic compound that has the formula $C_9H_{10}O_3$, and which he provisionally called *parahydrocumaric acid.* This observer points out here that the substances that result from the growth of the *Penicillium glaucum* and other moulds have diverse chemical peculiarities, depending on the culture medium, the length of time that the culture is allowed to develop, the amount of oxygen admitted, and the heat, light, etc., to which it is subjected; it is likewise true that the phenol compounds are formed probably in series, and that, therefore, the nature and quantity of the aromatic substances present in a given culture will depend largely upon the stage of development of the organism when the examination is made.

In the course of his investigations Gosio (6) likewise detected a substance that seemed to be cumarine, and which appeared to be united with ammonia; it is liberated when treated with an acid, and then may be extracted with ether; on evaporation the fixed cumarine remains, and gives on the addition of an alkali a most beautiful rose color, which varies to purple and violet, and at the same time there are produced the characteristic odors that occur under such circumstances. That this substance is cumarine is further shown by the fact that the color disappears on the addition of an acid and returns on realkalinization, or, in case a volatile acid has been used, on the application of heat.

There was a substance discovered by this investigator (8) that resembled phytosterin; this body crystalizes in small needles, is insoluble in water but soluble in boiling alcohol, ether, chloroform, and benzol, and fuses at 141° C. (375° F.). This substance is not poisonous. It bears in its formation an inverse relationship to the production of toxines, not being formed at all or only in traces where growth occurred at 23° C. (73.4° F.), but to the extent of from 5% to 6% where it was at 37° C. (98.6° F.).

The technic of Gosio's test is described on page 349.

The results obtained by Gosio are in the main confirmed by his student, Palladino (2, 3). He believes the toxine to be volatile, though he mentions that Bodin and Gautier have insisted on the damaging effects of heat on the poison of the *Aspergillus fumigatus* after a temperature of 85° C. (185° F.) has been reached, and with this Palladino entirely agrees. He criticises Ceni for his obstinately asserting that the toxines of moulds vary with the season, and strongly maintains that the period of the year alone has no influence, but that the variations that undoubtedly occur are the consequence of the different temperatures at which the moulds grow.

Ceni alone, and in collaboration with Besta and Costa, has written a large number of papers on this subject. Ceni and Besta (1, 2, 4) prepare the toxine from cultures of the aspergilli by extracting with ether for 12 days at ordinary temperatures or with 90%

alcohol at 38° C. (100.4° F.); the alcohol on being separated and evaporated down leaves a greasy mass, from which the toxines are obtained by dissolving them in water. They obtain the toxine from the penicilli by extracting with boiling 90% alcohol for at least 30 minutes; they say that the depressive poison is insoluble, and the excitive poison soluble in water. These substances are quite resistant, not being destroyed by the boiling temperature for 20 minutes, nor are they affected by alkalies, according to these writers. Out of 107 examinations of cultures of penicilli Gosio's phenol reaction was found by Ceni (12, 15) positive only 36 times; indeed, he asserts that in seven instances where the toxin was present, no phenol could be discovered. He (18) claims to have found poisons in cultures of *Isariae* and *Citromycetes*, which were obtained from decomposing maize, and described (20) a new *aspergillus* which he calls the *Aspergillus bruno gigante*. His toxines were obtained from cultures of the *green penicilli*, and from *Aspergillus fumigatus, flavescens, varians* and *ochraceus*. This author is by no means always accurate, as he (13) once wrote an article on a new *species* of *Aspergillus varians*. He (22) found poisons in other culture media than maize, obtaining them from Raulin's liquid, and from media in which the carbon content was made up of various starches; in one instance he found a depressant poison in gorgonzola cheese. He (21) likewise claims to have determined that penicilli which produce during their growth no poisons in Germany acquire this property when cultivated in Italy.

He (26) observed that the formation of toxines was influenced by light—the different rays varying somewhat in their action; thus it was found that the violet rays inhibit the development, but do not modify the toxines or the chromogenic power of penicilli; on the other hand and red rays influence the formation of colors, but do not affect the toxine. He (17) showed that there is a relationship between the vigor of growth of moulds and the amount of toxins they produce.

Ceni's (9, 11-18) chief claim to original research in this connection has as its basis his observations on the seasonal variations in the toxicity of different moulds, but as has been already pointed out, precisely similar observations were made some 15 years earlier by Husemann, and although this writer was given no credit by Ceni for the discovery, it is hardly likely that such a student of this subject as this writer evidently is, could have overlooked the work previously done along these lines. In the face of what appears overwhelming evidence to the contrary, it does not seem possible, furthermore, for Ceni to sustain logically his often expressed opinion that these variations in toxicity are purely the consequence of season; on the other hand, almost certainly such changes as do occur are occasioned by variations in temperature.

Ceni has at no time made any pretence of thoroughly studying the chemical nature of the toxines with which he was working, so that he has added practically nothing to our knowledge of this phase

of the subject. The only attempts which he has made to differentiate between the various toxines have been based on their solubility in various media, and on their physiologic action—criteria which are not by any means distinctive, as it is well-known that most substances dissolve in the usual solvents, and differ widely in their action, depending upon the concentration and the amount given; there is, indeed, much reason for the belief as pointed out by Gosio (7) that the two poisons which have been uniformly claimed by this writer as the result of mould activity are, after all, one and the same. While it is admitted by Ceni that there is no fixed rule, in a general way he has contended that moulds produce a convulsive poison in the spring and summer, and a depressive one in fall and winter.

One of the most interesting of recent papers on the mould toxines is the brochure of Alsburg and Black. These investigators studied five different species of spoiled maize from the southern part of the United States, and found that two produced toxic substances. When tested with ferric chloride one gave a brown, two a faint brown, another a brick red color, while a fifth showed no change; the first of these was one of the toxic organisms, and was identified as *Penicillium puberulum* Cainier; the last named organism was then carefully studied and it was found that it produced a toxic substance quite independently of any acidity of the medium, and occurred in far greater amount on meal mush than on Raulin's liquid. The reddish color just referred to was not given by the germ itself, but by its extracts. The substance producing this reaction was isolated and found to be soluble in chloroform, and it produced crystals which were large, transparent, biaxial, monoclinic or triclinic, and rhombic. It burns without leaving ash, contains no nitrogen, and is optically inactive; it is acid to litmus and phenolphthalin, and decomposed carbohydrates at ordinary temperatures. The crystals melt at from 64° to 65° C. (147.2°-149° F.), and the anhydrous substance from 86° to 87° C. (186.8°-188.6° F.). It was found to have the empirical formula $C_8H_{10}O_4$, and appears not to have been heretofore described. It was called *penicillic acid.* It reduces Fehling's solution, is fairly resistant to acids, but is very sensitive to alkalies. With dilute ammonia it gradually assumes a deep red color. It does not give alkaloidal reactions. Liebermann's reaction occurs as a beautiful carmine red, while Millon's reagent produces no change. The substance closely simulates the *lichen acids,* and both resemble Gosio's aromatic compound, having closely similar empirical formulae and properties. There was also found evidence of other substances in the cultures, there being traces of *acetaldehyde, acetic acid, glycerine,* and *succinic acid.* They note that penicillic acid, and many lichen acids, react in the same way as DiPietro's supposed glucoside. They also observe that the latter substance gives reactions with ferric chloride very slowly, in which it exactly resembles penicillic acid. DiPietro's glucoside loses its reducing power after being boiled in acid solutions, but not in neu-

tral solutions; penicillic acid and lichen acids behave in the same way. This supposed glucoside also decomposes on being boiled with acid, it being supposed that its sugar is split off by hydrolysis and an aromatic acid set free, but it is likewise true that penicillic acid behaves in the same way under similar circumstances.

It is interesting to note that these writers have determined that the amount of penicillic acid formed in culture is largely dependent on the amount of oxygen present—either too much or too little of this substance preventing its formation; this, the writers think, probably explains many of the discordant results heretofore obtained. The form in which nitrogen is offered likewise influences the result, as the acid is not formed when the only source of this substance is tyrosin or lucin. Penicillic acid contains more oxygen than the compound isolated by Gosio, which may account for the fact that the former is toxic and the latter is not, for it is well-known that the introduction of hydroxyl into the benzol ring increases toxicity. Penicillic acid is rather unstable, decomposing at the boiling temperature. They found practically the same amount of acid every month of the year.

These writers further studied the *Penicillium stoloniferum*, which was obtained from Italian maize. The cultures from this organism gave the typical violet reaction described by Gosio when treated with ferric chloride. The substance giving this reaction was obtained and purified as follows:

The culture fluid and mycelii were transferred to an evaporating dish and rendered weakly alkaline with sodium carbonate. The content of the dish were then heated to boiling and filtered hot, the mycelii remaining on the filter being thoroughly pressed. The mass was then again thoroughly extracted with water and rendered weakly alkaline with sodium carbonate. The combined extracts were evaporated to a small bulk over a free flame and filtered hot. To the clear filtrate a slight excess of hydrochloric acid was added, which produced an abundant precipitate, consisting of a mixture of needle-like crystals and amorphous material. The precipitate was separated by filtration and washed in cold water, and after drying spontaneously it was extracted with hot toluene and the hot extract filtered; only the crystalline portion of the precipitate dissolved. The amorphous dark brown material that remained on the filter was discarded, for it did not give a color reaction with ferric chloride. On cooling and evaporating the toluene extract spontaneously precipitated in the form of needles, the material gave the ferric chloride reaction. These needles, which were still slightly colored, were finally obtained white either by decolorization with bone black in hot toluene solution, or by dissolving in alcohol and then adding alcoholic potassium hydroxide to form the potassium salt, which is insoluble in alcohol. This salt is then washed free from color with alcohol. From the potassium salt the free acid is recovered in the form of white needles by dissolving the salt in water and precipitating with hydro-

chloric acid. The substance thus obtained was named *mycophenolic acid* ($C_{17}H_{10}O_6$).

This acid melts at 140° C. (284° F.), is insoluble in water, but freely soluble in alcohol, ether and chloroform, and somewhat less soluble in benzine, moderately soluble in cold toluene, and very soluble in hot toluene. With ferric chloride it gives a violet color in aqueous solution and a green color in alcoholic solution. It does not give Millon's or Liebermann's reaction, nor does it reduce Fehling's solution or ammoniacal silver nitrate; it is fairly resistant to ordinary alkalies and acids, and does not readily decompose carbonates at ordinary temperatures. It is apparently a dibasic acid, giving two series of salts. Like Gosio's substance, it is not toxic.

As regards the much mooted question as to whether the phenol poisons are present in the culture or in the culture medium, the writers make the interesting suggestion that this depends possibly on the reaction of the medium. When the poisons are insoluble acids, but which like mycophenolic acid form soluble salts, they will probably be found in the mycelium when the medium is acid, and dissolved in the culture fluid where the latter furnishes a base with which it may unite.

The writers remark that it is very strange that we do not find Gosio's violet reaction more common in this country, inasmuch as the *Penicillium stoloniferum* is not at all uncommon. A culture of this germ from American sources, growing side by side with strains obtained from Italy, produced substances in the medium that gave reactions in every way similar, but most curiously when the writers attempted to separate the mycophenolic acid from the former, none could be found—there being in its place a set of quite different substances.

The writers wind up by the suggestion that we may perhaps ultimately be able to distinguish the different moulds by their metabolic products.

In 1906 Otto wrote an interesting paper, in which he showed that cultures of *Aspergillus fumigatus* gathered in various parts of Germany proved on cultivation incapable of producing toxines, while on the other hand traces of poison were found in cultures of *Penicillium glaucum*. This observer found the toxine almost exclusively in the mycelii, though traces of it are present in the spores.

Gavina (1, 2) has written several articles, in which he clearly shows that the toxines are present in the culture media—at least during the period of their development, at which he made his examinations; Antonini and Ferrati are entirely in accord with Gavina on this point.

Audinino has written a most excellent paper on this subject; he thinks pellagra, if not produced, is at least aggravated by *zein*, and he is furthermore of the opinion that inasmuch as a number of bacteria undoubtedly develop in maize the toxines must vary accordingly. He agrees, however, that the principal ones are *glucosides* and *phenols*.

In 1907 Antonini (8), in discussing Gosio's paper at the meeting of the Third Italian Pellagra Congress, mentions that on the suggestion of this investigator he had fed a dog for some time on a purely vegetable diet, consisting of cabbage, rape, potatoes and beans, with a little grease to make it appetizing; after a time the dog presented symptoms similar to those that are encountered where bad maize is given. This result is most curious, and cannot be accounted for by any of the usual theories; certainly they cannot be the consequence of monophagism or vitamine hunger. On the whole this experiment would seem to show that changes in nutrition followed by physiologic phenomena occur when an animal is kept for a long period of time off of its natural food—which is precisely what occurs in the Italian peasant when he lives practically the year round on maize mush alone.

As noted in speaking of the enzyme theories of pellagra, Camurri (7, 8) has recently strongly urged that the real pellagrogenic agencies are ferments—a large number of which are undoubtedly present in mouldy maize. There can be no doubt that if these bodies are absorbed that they would give rise to pronounced pathologic changes.

Source and Method of Production of Maize Toxines.

From the foregoing we may safely assume that it has been demonstrated that the toxic substances present in bad maize products vary widely under different circumstances. It is clear that a great number of true bacteria may under appropriate conditions develop in Indian corn, with a production of their specific poisons, but it may be well doubted whether these substances are formed in sufficient quantity, under ordinary circumstances, to play an important rôle in the toxic states that follow the ingestion of bad maize products. On the other hand bacterial toxines, even though occurring in small amount, must necessarily be harmful, and doubtless in influencing the health in a detrimental way play a more or less important part in coloring the clinical picture of any disease from which those who ingest them may be suffering. As to the questions how and from what constituents of maize these substances arise, ignorance must be confessed, but it seems not improbable that they come in the main from the nitrogenous elements of this cereal. In this connection it is important to remember that pellagra varies at different times and in different localities.

It should likewise be remembered that, as already shown, a deleterious action is probably exerted by certain normal constituents of maize—notably zein—and that in addition the organism must of necessity be unfavorably influenced by the indigestibility of the constituents of Indian corn.

It having been, however, clearly determined that the principal toxines that are produced in maize are unquestionably the result of the life activities of different species of hyphomycetes, the question next arises as to whether these substances originate from the moulds directly, or whether on the other hand they come from a trans-

formation of some of the constituents that go to make up the cereal upon which they develop. Like most other questions connected with this subject, there have been as many different views as there are possibilities, along with but little attention to the facts demonstrated by those who were willing to throw theory aside and to try to find out the truth by careful experimentation.

In the very beginning of his work on the toxines of hyphomycetes Gosio (1) stated—and gave very good reasons for the assumption—that the principal poison is the result of a decomposition in the starches of the grain produced by these organisms, and if such be the case it would seem probable that they do *not in the main arise directly from the moulds themselves.*

On the other hand several of the earlier writers on this subject were of the opinion that the poison resides almost entirely in the *spores of the moulds*—Ceni (8), Ceni and Besta (1), Besta (1), and DiPietro (5), especially holding this view.

Somewhat later it was asserted by Besta (5) and Otto that the toxines are produced both in the *spores* and in the *mycelii*, the former declaring that they reside mainly in the spores, and the latter in the mycelii.

Neither of the two views last mentioned, however, has gained general acceptance, practically all of the recent experimenters agreeing with Gosio. Thus we find Bodin and Gautier, Antonini and Ferrati, and Gavina (1, 2), as the result of most careful investigation, coming to the conclusion that the mould toxine in reality occurs in the culture medium, and that it is not produced in the mould organism. As an explanation of the conflict of opinion that has arisen on this subject may be mentioned the observation of Audinino that the results depend largely upon the age of the culture; thus we found that in the beginning the toxine is in the mould stratum, somewhat later in the liquid that lies beneath, and finally in the meal at the bottom; occasionally it is found in all three.

It is likewise almost certain, as was suggested by Besta (5), that these various investigators worked with different poisons. As was early pointed out by Gosio (1, 2, 8), the substances resulting from the life activities of the moulds likely form a series of aromatic compounds, and it is, therefore, more than probable that the toxines obtained in some instances differed from each other. This is all the more probable when we consider that the various workers have employed different strains of the germs, that few, if any, were examined at precisely the same stage of their growth, that the culture media were probably never exactly the same, and that the amount of oxygen and the physical conditions were never quite identical, which, in addition to the varying methods employed for obtaining the poisons, seem quite enough to account for discrepancies of this character. The reaction of the culture medium may also affect the solubility of the poisons, since it was noted by Bodin and Gautier that the media only became poisonous with the development of alkalinity, and likewise the phenol toxines found by Alsberg and Black

in mouldy maize dissolved in aqueous solutions only when the medium became alkaline. Under such circumstances soluble salts of the phenol acids form—a transformation that cannot occur as long as stronger acids are present. On the other hand the toxin found by Gosio (1, 2) could no longer be found after the reaction became neutral or alkaline. Only Ceni and Besta (1, 3, 4) found a poison unaffected by the reaction of the culture media.

As it would appear from the foregoing that the mould toxines are produced in the culture media, the question next arises: From which of the component parts of maize are these substances derived? Fortunately the comparatively simple chemical composition of Indian corn makes the answer fairly easy. Outside of the husk, which is largely made up of cellulose and inorganic constituents, and which it is not necessary here to consider, we find that the organic elements of the grain consist of *fats*, *albumins* and *starches*, and it must, therefore, be from one of these that the toxine takes its origin.

The theory that *fats* are in some way associated with pellagra is almost as old as the descriptions of the disease, it having been first suggested in 1776 by Albera, and later frequently referred to in the writings of the pellagrologists of the nineteenth century. More recently the theory has been rediscovered in America, cottonseed oil being particularly inculpated. There is, however, nothing in analogy or in observed facts whereby this view could be substantiated, and it is inherently so improbable that it scarcely deserves discussion in this connection. It is true that decomposed fats, like other foods in a similar state, are probably unwholesome, and, indeed, we have the testimony of Faust, who experimented on dogs with fatty acids, that the continued administration of considerable quantities of such substances acts in a deleterious manner upon these animals. However, so far as the mould poisons of Indian corn are concerned, this matter has been definitely disposed of by the observation of Gosio, who showed that identically the same toxines are produced by the action of hyphomycetes on maize, whether the fats normally present in the grain are removed or not. It should be noted in this connection that these poisons are quite soluble in oils, and that, as a consequence, maize oil might show toxic properties when taken from this cereal in a mouldy condition. As respects the possibility of the formation of poisons from the *albuminous* portions of the grain, it must be at once admitted that, *a priori*, the probabilities of this occurring are much greater than is the case with the fats, but it is rather singular than no one appears to have seriously put forward the view that this is the case. True, we find Terni (1) maintaining that the toxic moulds by preference attack the aleuronic portions of the cereal, and even asserting that little or no poison is produced in the endosperm which contains only a small quantity of protein substance. But mention should be made of the fact that this author gave no experimental data as a basis for his views, and as he appears to be the only writer who holds them, there seems no good reason at present for giving his opinion

further consideration. The chemical composition would further indicate that the mould toxines are not produced from proteids, it being in the highest degree improbable that aromatic poisons originate from substances of this character.

From the foregoing it would therefore appear certain, leaving aside the possibility of toxic enzymes, that these poisons take their origin from *starches,* as was in the beginning thought by Gosio—there being here then an instance of transformation from the fatty to the aromatic group of carbon compounds.

That moulds possess the power of bringing about changes of this character there seems to be no doubt, it being, indeed, claimed by Gosio (1) that this is one of the special peculiarities of this group of vegetable organisms. That moulds do exert a destructive affect on starchy substances is well known. This is evidenced by the curious experiment of Naegali. This investigator placed some pieces of bread in a tin box which was accurately but not hermetically sealed. After one and a half years the box was opened, and the bread was found reduced to a small mass that consisted almost entirely of filaments of the mould that had destroyed it, and in which no traces of starch could be found; what remained gave the strong odor of trimethylamine.

A similar experiment was made by Gavina (3), who took 100 grams of maize meal that consisted after desiccation of 63.08% of starch, and 9.55% of nitrogenous material, and after sterilizing added to it 30 grams of water, and then inoculated it with the spores of *Penicillium glaucum.* The culture was examined, apparently, about six weeks later, and it was found on drying that it contained only 18.22 parts of starch and 6.33 of nitrogenous substance.

Gosio (1, 2), who particularly called attention to the fact that the poisons of bad maize are the result of the life activities of moulds, has also shown that similar poisons are produced when these organisms are grown on other carbohydrates, including cane sugar, glucose, dextrin, dulcite, milk sugar, maltose, mannite, etc.

As to how this action is brought about there is little doubt, as it is universally conceded that it is not generally the direct consequence of the action of the moulds, but is the result of the enzymes which they produce. True, it may be possible that in the very earliest stages of their growth, while the enzymes are within the mycelii, carbohydrates may be absorbed by the plant, and that the transformation may take place within its tissues; at a later time, however, as has been shown, there is an abundant secretion of saccharifying ferments into the culture medium, and it cannot be doubted that the major portion of enzyme action is exerted during and following this period. As evidence of the truth of the foregoing statements are the investigations of Bechamp, Gayon, Ducleaux, Herissey, Gerard, Dox, and more than all, of Bourquelot; it is of interest to note that Hansen, Wehmer, Bourquelot and Herissey, Malfitano, and Steffens, have demonstrated proteolytic ferments in penicilli and aspergilli, and that Gerard and Camus and others have likewise

found in these organisms a *lipase*. In his recently published and very careful study of the enzymes of the penicilli and aspergilli Dox mentions that *protease, nuclease, lipase, emulsin, amylase, inulase, raffinase, sucrase, maltase, trehilase, gentianase, melizitase, amivase, zymase,* and *oxidase* have been obtained from these moulds; *lactase* is said to occur also when *lactose* is the source of carbon in the culture medium.

Dox has also studied the mould of Camembert cheese *(P. camemberti)*. This germ was grown on a medium in which *sucrose* was the only source of carbon and sodium nitrate the only source of nitrogen, and it was found that these moulds produced the following ferments: *erepsin, nuclease, amidase, lipase, emulsin, amylase, inulase, raffinase, sucrase, maltase,* and *lactase*. This writer observed that *erepsin* is formed independently of the presence of protein or protein derivatives in the culture medium. He also noted that the carbohydrate splitting enzymes, *amylase, inulase, raffinase, sucrase, maltase* and *lactase* are formed, no matter which of the corresponding carbohydrates has served as the source of carbon in the culture medium.

From the foregoing investigations it is evident that these moulds produce enzymes that act on carbohydrates, proteids and fats, and that under proper conditions we should not be surprised at the production of any possible corresponding derivatives of these substances. Gavina (3) has shown that they produce toxines in starches, even after the organisms that elaborate them have been removed.

The studies which have been made of moulds in relationship to their probable connection with the production of the pellagrous poisons have brought out a great many interesting facts respecting their life history. It was early shown by Gosio (2) that cultures of the *Penicillium glaucum* by no means uniformly produce toxic substances, and he stated in the same paper that where this organism shows but slight powers in this direction, their capacity to cause such changes may be materially increased by appropriate surroundings, particularly as regards temperature. In later papers this view was further emphasized, and this investigator showed in addition that light, the character of the culture medium, and the amount of oxygen present is also of importance in this connection.

At an even earlier period Husemann had asserted that the character of the poison produced by the moulds in bad maize varies greatly, there being formed primarily and under all conditions a narcotic poison which occurs in increased amounts in the autumn and winter months; in addition there is found in the summer a toxine still more potent, which has a strychnine-like action; this writer also mentions the possibility of a third toxine, which would appear to produce cramp-like contractions of the flexors.

Within recent years Ceni (9, 11-18), and Ceni and Besta (1-4), have taken to themselves credit for this observation, and they maintained that these poisons are produced purely as a consequence of some mysterious influence exerted by season, without the tempera-

ture or other conditions in any way affecting the results. On the other hand Gosio and Palladino have maintained that the seasonal variation in toxicity of moulds is on the whole largely a question of temperature, though they likewise suggest the great probability that such effects have often been the consequence of the culture media not being the same, and that other changed conditions are frequently responsible in a measure for the result attained. It is likewise pointed out by Gosio (7) that many drugs act in contrary ways, depending upon the amount administered, and he is strongly of the opinion that the variations in effects produced by mould toxines have been often influenced in like manner.

One of the most curious facts shown by recent investigation is that it would appear to be true that the same species of moulds vary in their capacity to produce toxines in different countries. Thus it was found by Otto that in two cultures of *Aspergillus fumigatus* that were imported into Germany from Italy, poisons could be obtained from the cultures by extracting with either hot or cold alcohol. On the other hand five cultures of the same organism obtained in Germany were found to be incapable of producing poisons at all. He noted that the Italian cultures generated their poisons only in the summer months. He, however, found that twelve cultures of *Penicillium glaucum* that were isolated in Germany resembled the Italian organisms, with the exception only that they were less toxic.

The poisons found by this writer produced apathy and sleepiness, in no instance causing symptoms of excitation.

Ceni (21) investigated this matter still further by obtaining cultures of these moulds from various parts of Germany, and found that on being brought into Italy they acquired the property of producing in a perfectly typical manner the several poisons described by this writer.

Gosio (7) remarks that these results are not entirely out of keeping with what is established respecting other vegetables, it being known, for example, that no epiol is found in the parsley of Germany, while that of France contains 50% of this substance; on the other hand the former contains miristicin and the latter none.

From the foregoing it is quite clear that toxines form in maize and its various products, just as they do in other food substances. It is furthermore quite certain that these poisons vary, depending upon the organism, the life activities of which elaborate them. While maize may undergo pronounced bacterial fermentation under certain circumstances, it is obvious that the special conditions necessary for this to occur to any appreciable extent are altogether exceptional, and practically always artificial. As a consequence it is evident that poisons resulting from such organisms can play no prominent part in the production of pellagra, or other toxic states.

On the other hand the evidence is conclusive that a large number of different species of moulds find in maize ideal conditions for their development, and that as a result practically all of the products of Indian corn that come to our tables have to a greater or

less extent undergone the peculiar fermentation to which hyphomycetes give rise. As clearly shown in the preceding pages, fermentation of this character is, except in the hottest periods of the year, constantly associated with the production of toxic substances, and, as will be presently seen, these poisons in their action on animal organisms appear to fulfill every requirement as pellagrogenic agencies.

We may conclude with the assertion that it has been definitely shown that practically all maize products contain mould poisons, varying in amount in dependance upon the degree and character of the fermentative change that has taken place in the cereal, and that there perhaps also occurs to a certain extent, in addition, minute quantities of toxic substances that are of bacterial origin. It is of interest to note also that these mould poisons are only produced at those seasons of the year when pellagrous outbreaks usually occur, namely, in the spring and autumn.

PHYSIOLOGIC ACTION.

No attempt will be made to differentiate between the effects produced on the animal body by the different poisons of bad maize, as their individual action has not as yet been studied.

The first writer to test the physiologic effect of the poisons of maize was Balardini (1). He says:

"Mush made from meal of bad maize, prepared in the usual manner by means of water and a little salt, was boiled for a few minutes—the resulting compound having a greenish-yellow color in place of its usual golden tint, and emitting a disagreeable musty odor; the mixture was found to be acid with blue litmus paper.

"I, my elder son, and Dr. Grandoni, chemical pharmacist of the Hospital of Brescia, ate a small amount of this mixture on an empty stomach; it had a nauseating, bitter taste, and quickly produced a burning sensation in the palate and fauces, which extended down a good way into the esophagus, and persisted with much inconvenience throughout the day. With this burning there was quickly associated nausea, followed by belching and general discomfort, which was shared by the stomach, which bore badly this unhealthy food.

"The digestion following this was slow, and the effects already mentioned continued almost the entire day, with an unaccustomed, inexpressible feeling of malaise, which only slowly disappeared after dining in the evening. I suffered a certain amount of weakness of the entire body, which was true of my companions. During the whole time there was such a feeling of disgust that Grandoni, after repeating the experiments on the second day, did not have the courage to do so again, as was the case also with my son.

"I ate another time the ungrateful food in a less quantity, and had, as before, much the same symptoms already referred to." (pp. 94-95.)

The writer then goes on to describe a number of experiments which he made on chickens. He noted that although they ate this

maize greedily in the beginning, after a little time they began to reject the grains which were affected, and still later showed evidence of illness, standing quietly in their cages, with downcast look, and gradually becoming emaciated.

Balardini, in speaking further of the acute effects following maize intoxication in man, relates that he was informed by Dr. Gallizioli that the members of two families, after having eaten fermented maize for a time, showed *disturbances of the digestion, dizziness, a tendency to melancholy, general debility, headache, diarrhoea,* and other morbid symptoms, which continued until the cause of the trouble was discovered, and they returned to a normal diet.

In 1865 Tuccimei reported six cases in which severe symptoms of an acute character, somewhat resembling ordinary ptomaine poisoning, followed the eating of bad maize; five of these cases occurred in one family.

In 1869 the well-known pellagrologist, Lombroso (2, 3, 6 and 8), took up this subject and made a large number of experiments in both men and animals. He employed in his investigations fermented maize in the natural condition, and also its active principles, administered as a tincture, and found that 17 out of the 28 individuals upon whom he experimented showed the following extraordinary symptoms: *belching, prostration, drowsiness, diarrhoea, pyrosis, nausea, smarting in the fauces, headache, hunger, insomnia, thirst, pains in the limbs, confusion of ideas, sweating, dizziness, pruritis,* and *diminution in the bodily weight!*

Ten out of twelve persons to whom a tincture of bad maize was given showed after the 4th, 7th, 17th, and 30th doses, an action that was more decided than in the experiments just referred to, and which persisted for from two to nine months after the poison was discontinued; in these cases the clinical phenomena were: *hunger, diarrhoea, disgust for food, pruritis, desquamation, skin inflammations, burnings,* and *such nervous phenomena as headache, vertigo, ptosis, dilitation of the pupils, somnolence, a desire to contemplate and get into water, irritableness, and painful desire to weep without cause, and loss of the affections!* Truly most astonishing results! Can it be wondered at that Lombroso's claims met with much derision on the part of scientific men during the earlier period of his career?

Two other series of experiments were carried out, likewise with remarkable results. There was observed a *tendency to fainting, palpitation of the heart,* the action of which was first *increased* and then *diminished,* a *decreased urinary secretion,* with *higher specific gravity,* and a *loss of weight;* in one instance there was *increased appetite,* with actual *gain in weight,* and in another a similar result followed as the result of an old tetter being relieved.

Later, in conjunction with Erba, Lombroso separated from the tincture of bad maize a number of different substances, to which reference has already been made, and which were called by him *oleoresin, pellagrozeina* and the *glutinous substance of maize,* and

finally there was obtained from the cereal after the alcoholic extraction, a substance soluble in water, which he called the *watery extract of bad maize.*

The *oleoresin* showed a marked effect on animals, particularly acting on their central nervous systems, producing in quadrupeds lowering of the temperature, sleep, paresis, contractions in the extremities, and finally death.

The *pellagrozeina* was also found to be highly toxic, its affects being most pronounced when the animal was placed in a room at a high temperature. The poison produced had also a toxic affect on the nervous system, causing vomiting, contractions of the posterior extremities, dilitation of the pupils, exaggeration of sensibility, increased reflexes, and finally a general tetanoid condition.

The *glutinous substance of maize* was found to be physiologically negative.

The *watery extract of bad maize,* on being tested, showed a pronounced action on the central nervous system, producing lowering of the temperature and paralysis.

But little effect was produced on frogs by the injection of the first alkaloid-like substance isolated from bad maize, which, as previously stated, was obtained by Brugnatelli and Zenoni (1) in 1876, though the somewhat similar body isolated by Pelloggio in the same year was said to have produced *difficulty in breathing,* and *loss of vivacity* and *sensitiveness.* In 15 minutes *paralysis is complete,* and after 5 hours the animal *appears dead*—which is often the case. This substance acts in no way like strychnine.

Somewhat later Husemann obtained from fermented maize a *narcotic substance* which was mainly elaborated in the winter, and a *struchnine-like body* that was produced principally in the summer; he likewise mentions that there may be still a *third toxine* which has physiologic properties resembling nicotine.

Lussana and Chiotto likewise found *poisons* in putrefying maize and wheat, and Hofmeister extracted *toxic alkaloids* from decomposing Indian corn, which produced even in small doses slight narcosis and marked tonic and clonic spasms, resembling those caused by *picrotoxine,* though not entirely identical with them. (See Neusser, 1.)

Selmi obtained *acrolein,* which he remarked was probably united before extraction with ammonia. It produces a feeling of *pressure in the stomach, belching,* and in larger doses, *salivation, reddening and swelling of the mucous membrane of the throat,* and finally *convulsions.*

The toxine found by Neusser (1) in distillates from bad maize produced after a slight period of *excitation* the gradual appearance of *paralysis,* and finally *death in a narcotic state.* The writer remarks that this picture is less like that of picrotoxine poisoning than a toxic condition induced by solanin.

Much more carefully carried out were the experiments of Gosio (1-9) on the mould toxines of maize. In his first paper on the

subject he records that he himself took repeated doses of the poison; in ascending doses it caused *constant headache, vertigo, disturbances of vision,* and in some cases *difficulty in swallowing.* He likewise showed that it was poisonous to rabbits when injected into the blood vessels, and he observed that spastic phenomena were produced in animals by feeding extracts of both the *Penicilli* and *Aspergilli;* such symptoms are usually also accompanied by spastic paralyses. Some species, such as the *Aspergillus glaucus,* the *Aspergillus flavescens,* the *Aspergillus novus,* and some varieties of the *Aspergillus varians,* elaborate poisons that produce more pronounced *depressive states,* being, however, always mixed with *spasmodic phenomena.* The *Aspergillus niger,* when grown on Raulin's liquid, *produced sleep when administered to animals,* with, in addition, a slight *tendency to convulsions;* when, however, these germs are cultivated on maize they produce toxines that are *spasmodic* and *convulsive.*

It is of the greatest interest to note that his experiments on animals clearly showed that *immunity is not secured* by repeated injections of these poisons—there being on the contrary a state of hypersensibility produced in this way.

Very interesting are that writer's experiments with the silkworm. An alcoholic extract was poured on the leaves, upon which they were feeding, and it was noted that the worms not only showed spastic phenomena, but that later the full-grown butterflies into which they transformed themselves exhibited throughout life *tremors, and ataxias, and flew with uncertainty.*

This investigator also showed that a state of hypersensibility to these poisons is *transmitted from parent to offspring;* where the parent rabbits have been poisoned by mould toxines it requires only half the usual quantity of these substances to kill their young.

Gosio likewise noted that rats are quite sensitive to the poison.

Experiments conducted by this investigator indicated that while the poison had no cumulative effect in the proper sense of the word, even a single dose is followed by *increased* sensitiveness to its subsequent use, and there seems to be no doubt, as has just been shown, that the toxine has the power of producing permanent alterations in the bodies of animals to which it is administered, and that *symptoms persist throughout life;* these conclusions in connection with the demonstration that increased susceptibility is transmitted from parent to offspring are of the utmost importance, and in addition to being in every way in keeping with what we know of pellagra, are of importance as tending to reconcile many of the inconsistencies that have heretofore militated against the acceptance of the maize theory of the causation of this disease.

In 1895, Tirelli (2) made a number of experiments on animals by administering solutions of the toxins produced in bad maize as a result of the action of moulds. After being given, there is a quadrupled output of urea, and an increase in sulphates, with loss of weight in the animal corresponding; there were fever, psychic dis-

turbances, unconsciousness, epileptiform convulsions, mydriasis, vomiting, and incontinence of urine and feces; there were also increased reflexes lasting several days.

The substances studied by DiPietro (1-6) appeared to differ in some ways from those described by Gosio. The former writer maintains that the higher up we go in the animal scale the more pronounced are the effects produced by the toxine that he investigated; man, he holds, is particularly susceptible to this substance. In dogs, his poison, when administered by the mouth, *produces loss of weight, tremors, paralysis, exaggeration of the reflexes, obstinate diarrhoea,* and a *spastico-paralytic gait.*

The substance called *penicillic acid,* which was isolated by Alsberg and Black, from mould cultures, was stated by these writers to have a *salty, slightly bitter-weet taste,* and to be *irritating to the mucous membrane.* In its toxic properties it resembles in every way the other phenols, though it is by no means so powerful as were the substances described by Gosio, DiPietro and others.

The poison obtained by Gavina (1, 2) likewise acts on the central nervous system, producing convulsions in animals.

This chapter would hardly be complete without some notice of the great amount of work that has been done in recent years respecting the demonstrable reactions of the organism to mould toxines. A large number of investigations have been made respecting the formation of agglutinins, precipitins, complement fixation, the Abderhalden reaction, and immunity, but it cannot be said that we have as yet come to any very satisfactory conclusions. While it appears that agglutinins and precipitins, as well as those conditions that give rise to Abderhalden's reaction, occur in pellagrins, and may be induced in animals by the injection of maize products, their true significance is by no means clear, and appear to be of but little practical importance. At most these reactions would seem to be rather uncertain indications that the subject had been in the habit of eating Indian corn, and would appear to be associated with maize albumins rather than mould toxines. However, many interesting papers have been written on this subject by Devoto, Volpino, Mariani, Bordoni and Alpago-Novello (1 and 2), Rondoni, Cesa-Bianchi and Vallardi, and Ghirardini and Zuccari, to which further reference will be made in the Chapter on Diagnosis. All of these writers show that when animals are fed for a time on maize they develop a high degree of susceptibility to extracts of mouldy maize, if given subcutaneously, and also to the serum of pellagrins. As respects complement fixation, it may be said that this reaction is even more than ordinarily capricious in pellagrins, and clearly possesses no importance, either from a scientific or practical aspect.

The anaphylactic phenomena observed in pellagrins after the injection of maize extracts would appear to be associated with the albuminous principles of this cereal rather than the toxines from moulds, and are, therefore, probably of no particular importance; like the precipitins and agglutinins, they would simply indicate when

present that the subject had probably been recently in the habit of eating Indian corn.

As respects the possibility of producing immunity by injections of extracts of bad maize, the testimony of writers is not unanimous. It would seem that we could hardly expect anything of value from such a procedure, as what knowledge we possess of this subject would rather indicate that the opposite effect would likely follow, and that a state of increased sensibility would be produced. This matter will be again discussed in the chapter on treatment.

The various biologic reactions of the blood in pellagra are fully considered in the chapter on symptomatology, to which the reader is referred for further information respecting this interesting subject.

EXPERIMENTAL LESIONS PRODUCED BY MAIZE POISONS.

As shown in the foregoing pages it is unquestionably true that various low vegetable forms, and particularly moulds, when developing on maize culture media, produce poisons capable of setting up in animal organisms both acute and chronic toxic processes. For thoughtful students of pellagra, however, this could be regarded as nothing more than highly suggestive—it being absolutely essential, before we can regard such results as being of importance, that experimental lesions should have been produced in animals by these poisons, resembling in every important particular those found in pellagrins. While it can not be said as yet that this has been accomplished in its entirety, we have a number of respectable investigators who have discovered changes in the brain and cord of animals poisoned with these substances, the alterations described very closely resembling those found in pellagra. In this connection we should never forget the possibility of such pathologic changes being the result of monophagism, vitamine starvation, etc., and being by no means specific.

Of more importance is the valuable and suggestive work done by Ceni (2 and 3), who showed that when chickens are fed on bad maize, the hens lay eggs the chickens from which exhibit abnormalities of development, often to the extent of being monstrosities, in a large proportion of cases. Gosio (7) has also shown that the offspring of animals poisoned by mould toxins often plainly show the effects.

The first article dealing with this aspect of the pellagra question appears to have been that of Palladino-Blandini (1), which appeared in 1903; he fed four dogs exclusively on good maize, three of which died spontaneously, while the fourth was killed after a year—it being in a state of profound marasmus. During the progress of the experiments the animals showed many symptoms in common with pellagra. They became lean, often vomited, had alternating constipation and diarrhoea, lost hair, presented spots of dry eczema on the skin, became very weak, walked with uncertainty, lost every expression of vivacity, and their urine showed albumin and acetone. On post-mortem examination there were found ulcers in the intes-

tine, parenchymatous, glomerular and interstitial nephritis, necrobiosis of the medullary substance of the adrenals, and fatty changes limited to the zone of contact between the medullary and cortical substance, alterations of Langerhan's bodies of the pancreas, and, most important of all, degeneration of the ganglion cells of the cord, with beginning sclerosis in the tracts, atrophy and degeneration of the cells of the spinal ganglia, and sclerosis of the coeliac axis.

Frisco found varicose atrophy in the nerve cells of the brain in rabbits after having been fed for three months with mouldy maize.

In the same year Pighini carried out a number of experiments, using for this purpose, in one series, hypodermatic injections of a tincture made from cultures of *Aspergillus fumigatus,* and, in another, introduced into the peritoneal cavity of dogs a number of maize seed infected with this organism; the animals in the first series died in from four to twelve hours, while in the second they lived from fifteen to thirty days.

Microscopic examination of the nervous system after death, developed that the animals showed in the spinal cord evidence of a primary degeneration of a combined character, including the crossed pyramidal tracts and the fasciculi of Goll. This process may be either acute or chronic; in the former there is an initial alteration of the myelin and a varicose swelling of the axis cylinders, and accompanying this there is usually a marked disturbance of circulation, giving the appearance of an initial myelitis; these alterations develop in from four to twelve hours: the more chronic changes are characterized by pronounced alterations in the myelin, as shown by the method of Marchi, while with that of Weigert there is seen to be a beginning sclerosis, rarely accompanied by disturbance of circulation; these changes develop in from fifteen days to two months. The degenerative changes cannot be considered as systematic in the strict sense of the word. The writer says that the alterations are comparable with the changes found in the spinal cord in pellagra, which is true.

In 1904 DiPietro (6) observed an erythema, with loss of hair, in some rabbits following an attempt to produce in them an immunity by injecting increasing doses of the toxin of the penicillium.

In the following year Besta (2), and Ceni and Besta (5), reported the results of the microscopic examinations of different parts of the central nervous system of animals poisoned with *Aspergillus fumigatus,* and assert that the toxine has a direct affect upon the cerebral cortex, causing destruction of the cells, which is the beginning point of lesions which are also found in the cord. Working with the method of Donnaggio, Besta found degenerative changes in the pyramidal tracts up through the bulbar portions of the cord and into the peduncles. In a dog poisoned in this way—the examination being commonly made at the end of three months—there were found scattered throughout the cord plaques of sclerosis affecting mainly the white substance, though here and there more or

less alteration was found in the gray substance. Where the toxine of the *Aspergillius fumigatus* is employed, and the intoxication is acute, the lesions of the pyramidal tracts are constant, though they are not invariable where the *penicillium* is used; in chronic cases there is no observable differenec between the two poisons.

Two years later, Sereni experimented on dogs, using both good and bad maize, and in addition one animal was given daily a gram of the dry spores of a very toxic strain of the *Penicillium glaucum;* the animals were killed in from two to six months, and on examination showed most marked pathological alterations in the pyramidal tracts, which were bilateral and symmetrical. In the animals that were given good maize the lesions were of the same character as in those that received the mouldy cereal, but differed in that they were less severe. He employed for his histologic work the method of Donnaggio.

In connection with the author's theory that pellagra may possibly be in all cases hereditary, of great interest and importance would be a careful histologic study of the tissues of the offspring of animals poisoned by bad maize, with the idea of determining as to whether alterations may be transmitted from one generation to the next, as was shown to be the case with alcohol by Stockard and his associates. Such an investigation would go far toward definitely clearing up many of the contradictions that have in the past so greatly militated against a frank acceptance by many, of the mouldy maize theory of the causation of this disease.

We can not finally leave this interesting phase of the subject without calling attention to a remarkable paper by Rondoni and Montagnani, who experimented on animals with sound maize and showed that in this way a pathologic state may be quickly induced. As to whether this be the result of the slow action of some toxic substance or substances—such as small quantities of mould poisons which are even contained in the sound grain—or whether it be a vitamine hunger, the consequence of a possible poverty of these substances in this cereal, or the result of some unusual form of inanition, has not been determined. These writers clearly show that this result is not the consequence of simple inanition by comparing the effects observed with the lesions found in chronic starvation. They were likewise able to demonstrate differences between the alterations here encountered and those that occur in scurvy.

In guinea pigs fed for some time with sound maize degenerative but not systematized lesions were found in the central nervous system, associated with early cutaneous changes, exhibiting a marked seasonal tendency to modification, splenic atrophy, hyperaemia of the liver, with breaking up of the cellular columns, and certain alterations of the bones and possibly of the bone marrow. It may be here remarked that such changes correspond quite closely to those found in pellagra, but the two pathologic processes show a marked variation from each other in that in the disease last mentioned lesions of the digestive tract are quite constant and very pronounced.

It is of much interest to observe that the writers mentioned found also most pronounced lesions of the thyroid and adrenals, and likewise probably some hypertrophy of the pancreatic islets. In the adrenals there was found a reduction in the lipoids, with pronounced degenerative changes in the cortical cells, associated with a tendency to an increase in the connective tissue framework of the organ. In the thyroid the alterations are most pronounced, being principally distinguished by a marked tendency to sclerosis. More or less similar alterations were likewise observed in the spleen. Certainly the resemblance of the changes here enumerated to those that occur in the human being in pellagra is sufficiently pronounced to be most suggestive.

In a series of experiments carried out on six dogs by the author some years ago no positive results were attained so far as histologic alterations are concerned, though the examinations made were confined entirely to attempting to determine whether or not areas of sclerosis existed in the spinal cord. On the other hand the animals clinically showed symptoms which were highly suggestive. They became lean, weak, ataxic, and all presented dry eczemas, along with the loss of a great deal of hair, and all of the animals died within about a year.

While the symptoms observed and the pathological changes found in the foregoing experiments closely simulate those encountered in pellagrins, we should not forget that similar clinical phenomena have followed the long-continued administration to dogs of a purely vegetable diet, or, as shown by Blosser, from feeding on sugars (absence of proteids and vitamine hunger?), nor should we overlook the possibility that the morbid changes might after all be only an expression of a general autointoxication which conceivably might be brought about by an improper diet. On the other hand we can not forget what has been written on the supposed close relationship between maize and pellagra, that everything goes to indicate that the lesions of this malady are the consequence of a chronic intoxication, and the extraordinary resemblance between pellagra and the symptoms and lesions that are produced in animals by the consumption of mouldy maize.

Resume of Theories of Etiology—Author's Modification of Maize Theory.

Having now considered so far as known every theory of the slightest importance that has been heretofore advanced in explanation of the causation of pellagra, it would seem not inappropriate to present at this point a brief résumé of the conclusions arrived at, and to make certain suggestions which have occurred to the author as of interest in connection with them.

Some of these theories need scarcely be considered, since they hardly amounted to more than suggestions put forward at one

period or another, and were at no time seriously maintained by their proponents; examples of this kind are the atmospheric theory of Thouvenel, the water of vegetation theory of Rosier, the electrical theory of Vay, and more recently the filarial theory of Allessandrini, and the colloidal-aluminium salts theory of Allessandrini and Scala.

Of somewhat greater importance, but wholly lacking in proof, is the miasmatic theory formerly advocated by Jansen, and, somewhat changed in detail in order to conform to modern ideas, more recently by Sambon, according to which pellagra is the consequence of an infection, presumably of animal parasites, introduced into the human body by blood-sucking gnats. It is not here necessary to repeat the numerous arguments advanced against this conception, though it may be stated that notwithstanding the earnest efforts of many observers to establish its correctness no one has ever found the supposed parasite, nor does the distribution of the disease correspond to that of the alleged intermediate host.

The continued failure to find a parasite of any kind likewise militates against the idea first advanced by Titius that the disease is due to an infection propagated in the ordinary manner. Notwithstanding that at one time or another writers have suggested or strongly urged the casual relationship to this disease of bacteria (Majocchi, Carraroli, and Tizzoni), moulds (Ceni, and Ceni and Besta), and amoebae (Long), we still entirely lack any positive proofs that might go to establish such a connection. Not only has there been a complete failure to find any organism constantly associated with pellagra, but careful attempts to inoculate healthy persons from those having the disease have heretofore proved futile (Buniva, 1805-1808; DeRolandis, 1824 and 1828; Vigo di Biero, 1847). Furthermore, the entire absence of focal lesions in the bodies of those dead of this malady, and the general and uniform character of the degenerative changes which characterize it, together offer the strongest presumptive evidence that the disease is not associated with infection of any kind.

Much nearer apparently to the truth are the various suggestions made at one time or another to the effect that this malady is in some way associated with our food. Experiments made as far back as the close of the eighteenth century clearly showed that the outward manifestations of pellagra are greatly influenced by nutrition, it having been at that time clearly proved that a satisfactory regime is of the greatest benefit in bringing about an amelioration and oftentimes a complete cessation, for the time being, of the more obvious pellagrous manifestations. Notwithstanding the fact that subsequent observation clearly indicated that such effects are only transient, the idea that the malady is the result of malnutrition has been seized upon more recently and advanced as being new. This view has been strongly advocated in some directions, and while clinical experience clearly indicates that good food is of much importance in the treatment of pellagra, the hereditary character of the malady, its frequent occurrence in people in the best circumstances, the

nature of the pathologic alterations, and the total inadequacy of the experiments made with the object of proving its truth, clearly show that lack of proper nourishment can not be looked upon as the principal causative factor in the production of the disease. We should furthermore remember that improvement under proper and adequate feeding is common to most diseases—particularly those that are chronic—but this is far from proving that these affections are due to lack of good nourishment. Certainly it is true that many of the lesions so abundantly present in pellagra remain throughout life, and that no amount of good feeding can remove them. Likewise there is not the slightest proof that this disease is of common occurrence in many countries where the lower classes feed on the poorest foods—often in amounts much below what we generally assume to be the minimum nourishment required for the preservation of life—and where the unfortunate peasant subsists practically altogether on some cereal. It thus appears, from an experience which includes many peoples, and numbers almost countless, that pellagra can hardly be due to either a general lack of food or to the dietary being of a one-sided character, notwithstanding the acute and remarkably able arguments that were urged in favor of this view by a great many extremely clever and scientific writers of the past two centuries, among whom we should particularly remember Fanzago (1789), Facheris (1804), Morelli (1855), Lussana and Frua (1856), Gemma (1871-83), and Strambio (Jr.) (1890).

Closely related to the foregoing is the view recently advocated to the effect that pellagra may be due to a form of inanition which results from an absence of certain necessary component parts of foods, called "vitamines" by Funk. However, the objections urged against the theory just considered would likewise here apply, since after all the absence of these substances in the ordinary dietary would result in a peculiar but imperfect and ill-balanced nutrition. On the other hand we could not deny that the absence of vitamines might among our poorer classes sometimes act as a predisposing cause to pellagra, though the frequency of this disease among the very best people in the southern portions of the United States, whose ancestors have been in affluence for generations, would clearly indicate that such influences play at most only a subordinate rôle.

The like might be said of monophagism—which after all may be nothing more than the vitamine theory under another name.

While it is in all probability true that unleavened bread is not very digestible, and therefore not entirely wholesome, there is no basis for the theory that its constant consumption could cause pellagra, nor is there any shadow of proof of the view that the imperfect digestion of maize products may produce similar effects.

Of much more importance are the theories which assume that the various foods made from Indian corn contain poisons, since there is adequate proof of the fact that such substances do exist in well-nigh all of the various maize preparations which form the basis of the dietaries of the peasantry in several countries, and which are

used in the southern part of the United States almost universally by the rich and poor alike. Which of these poisons, however, is to be regarded as the pellagrogenic agency, we are not entirely sure.

We may, of course, throw out of consideration the theory of Pari, according to which the parasite of maize "smut" gets into the kitchens of those living where this cereal is grown, and becoming mixed with the various foods, acts in such a way when eaten as to cause pellagra.

Likewise we may equally reject the recently advocated photodynamic theory, which seems to be sufficiently answered by calling attention to the fact that the disease is quite as common among blacks as whites.

Of much greater importance is the theory, now substantiated by an immense amount of most careful and accurate investigation, according to which this disease results from the consumption of certain poisons that are produced by the life-activities of low vegetable forms. While it is agreed that bacteria play a certain part in the production of the toxines encountered in maize products, the view which would assign to them a prominent rôle in the causation of pellagra has been abandoned. On the other hand, as has been abundantly shown in the preceding portions of this work, toxic substances, produced by moulds, and belonging to the phenol group, are probably always present to a greater or less extent in food products from maize by the time they reach our tables, and it is to these substances that the great bulk of European pellagrologists have turned for an explanation of the production of this terrible malady. In addition there seems to be some scientific ground for the opinion that the albuminous components of Indian corn lack certain important constituents that are necessary for the growth and even for the maintenance of life, and it is furthermore believed that at least one of these substances is mildly poisonous. When we remember that endemic pellagra, which includes practically all of the typical forms of the malady, occurs in maize eating districts, and has always been closely associated with this cereal and never occurred before its introduction as a food, it seems almost certain that there is some close connection between them.

That Indian corn contains toxic ferments seems highly probable, since the experimental proof of their presence appears to be conclusive; as to whether they may cause pellagra, however, there remains much doubt, though it is possible that they may play a subordinate rôle in the production of this disease.

We may then look upon pellagra as being a disease probably the result of the consumption of Indian corn which has undergone more or less fermentative change as a result of the life activities of certain moulds, and which is believed by many to be directly caused by a group of phenol poisons; in addition we have a variety of noxious influences that quite conceivably, nay even probably, play a more or less important rôle in its production, such being the failure of maize to supply, in ordinary quantities, a sufficient amount

of necessary nitrogenous nutriment, the presence in it of albuminous principles and toxic ferments that are mildly poisonous, the possibility that it has a low vitamine content, and a lack of digestibility, which is thought by some to be accentuated by its being quite universally eaten in the form of unleavened bread or as imperfectly cooked mush or grits; when, finally, we remember that in many parts of the world Indian corn constitutes almost the entire dietary of a large part of the population, and that as a consequence there must result all of the ills that necessarily accrue from monophagism, it is not difficult to understand why, when other well-known facts are recalled, the great bulk of scientific opinion turns to this cereal as offering the best explanation for the occurrence of pellagra. Certainly it would be most extraordinary for the human body to suffer no ill consequences from being subjected daily, from childhood to old age, and for generation after generation, to several mild but decided poisons, and a group of deleterious influences, which investigation has shown to be alone quite sufficient to set up pathologic processes in animals.

However, it was quickly seen that there are certain objections to this theory, which have appeared to many as well-nigh insurmountable.

While it was generally admitted that pellagra was a new disease and that in its typical and endemic form it only occurred where Indian corn was commonly used as a food, it was urged with truth that there were a few communities in which it did not occur, notwithstanding the fact that this cereal formed the basis of the dietary of the poorer classes—even, as in America, where maize had been used as a food for several generations.

It was furthermore asserted that pellagra has occurred in individuals who had never eaten Indian corn, and who resided both in countries where the malady does and does not occur, and where maize is and is not eaten.

It having been early observed that the disease is hereditary, many writers likewise objected to the maize theory on account of the presumed impossibility of toxic influences descending from parent to offspring.

There were in addition other apparent inconsistencies of less moment which have been discussed in the last chapter, but it appeared, if the foregoing objections could be answered, that the main difficulties which stand in the way of the acceptance of this theory would be cleared away.

For a long time an entirely satisfactory explanation appeared to be almost hopeless, and it was only after the author had spent many years in studying the history of the disease, and more particularly after a most careful investigation into its pathological anatomy and histology, that light began to dawn. The matter, however, ultimately seemed to become quite clear, and it appeared that at least in so far as the objections heretofore urged against this theory are concerned we have a perfect answer. It is, of course,

recognized that this does not necessarily imply that the author's modification of the old mouldy maize theory, which will presently be discussed, settles definitely this most complex question, for it may well be that there are difficulties of which we have not as yet taken cognizance, and that the whole idea might any day be completely upset by new additions to our knowledge.

After long consideration it seemed very clear that the frequently hereditary nature of the affection, and its extreme chronicity, as clearly indicated by the protracted clinical course and by the pathologic alterations, preclude the possibility of the malady being the result of an acute intoxication—which conception seems to have been the great stumbling-block in the way of the explanation of pellagra as being the consequence of maize poisoning. On the other hand, if we assume an exceedingly chronic process, many of the difficulties at once disappear. But even a chronic intoxication lasting from childhood to old age did not appear capable of causing this disease in a single life time, for there are well authenticated instances where maize has been daily eaten by the inhabitants of a community throughout their entire lives without the affection having made its appearance. Indeed, in America, where this cereal has been commonly eaten by our people for generations, there is grave doubt as to whether pellagra occurred up to within a comparatively recent time. True, we have had reports of a few supposed cases here and there in the past, but, in most instances those which were given in anything like sufficient detail to permit us to draw conclusions as to their nature, originated in non-maize-eating districts. While it is recognized that sporadic cases may have occurred in the southern portion of the United States from time to time during the last hundred years, we are far from certain that this is the case. In the records of the State Sanatorium for the Insane of South Carolina, that patient delver into the past, Babcock, has discovered histories that seem strongly to indicate that the disease was occasionally present in that State as far back as 1825, but unfortunately we can not be certain of this. Pellagroid symptoms are certainly common in the insane, even where there could be no probability that their mental state has any connection with the poison that produces this disease, and the author feels that a diagnosis of pellagra, under such circumstances, could hardly be considered as well authenticated. Even an erythema of an apparently characteristic nature could never be regarded as having a definite meaning without the records are clear as to the precise method of the onset—particularly in the absence of an early history clearly indicating as to whether the patient had suffered from the symptoms that occur in the first stages of the disease. Even the addition of disturbances of the gastro-intestinal tract could not be accepted as conclusive in the absence of such accurate data. As evidence of the extreme infrequency of pellagra in the past, at least in Georgia, we have the well authenticated fact that no case of insanity in the negro had ever been observed in our State Asylum

prior to the War Between the States, which occurred in the early '60's of the last century. We may then assume that maize was probably eaten for a century or more before pellagra made its appearance in the United States, and that it certianly did not occur to any extent until an even later period. It is likewise true that this affection did not occur in either Spain, France or Italy until the inhabitants of the regions where the malady subsequently developed had been in the habit of eating much maize for several generations.

In view of the foregoing facts it occurred to the author that inasmuch as statistical records of Italy clearly show that about half of all pellagrins appear to inherit the disease from their parents, *why can it not be true that pellagra is always hereditary?* It is well established that the disease may occur without skin eruptions or any of the classical symptoms, and under such circumstances it seems not unlikely, and certainly not impossible, that such victims of the affection, notwithstanding that they have failed to exhibit the usual symptoms of the malady may easily be poisoned to a sufficient extent to transmit the affection to their offspring. The author then would suggest that the first maize eaters probably never suffer from pellagra at all, but notwithstanding this that the poison produces an impression which is transmitted to their descendants, becoming more and more pronounced as this practice is continued from generation to generation. Where the people do not live entirely on this cereal and have an abundance of other food—as was the case in the United States—it may be that for a long time few or none are actually attacked by the typical symptoms, and where the conditions are favorable possibly three, four, five, or even more generations may live and die without the noxious influence of the maize poisons having been fully felt.

That intoxications show an extraordinary disposition to be transmitted by heredity is well known. We have seen, for example, as shown by Kussmaul and others, that mercurial poisoning, with all of its symptomatology, is not uncommonly found in children the offspring of parents who are sufferers from the toxic effect of this substance. Likewise it is generally conceded that the children of alcoholics not infrequently exhibit signs of disturbances which together are usually regarded as evidence of degeneration. Since the author's modification of the maize theory was formulated, curious and most important confirmation of the principle involved has appeared in the investigations of Stockard and Papanicolaou. These observers have shown that when guinea pigs are subjected to the poisonous action of alcohol by inhalation, little if any noticeable effect is observed in these animals, though there is some injury to their corneas and respiratory mucous membranes which is evidently the result of the direct action of the drug; however, the animals remained strong, active and healthy, and lived quite as long as those used as controls. Notwithstanding this very feeble immediate toxic action of the drug, their offspring showed most pronounced ill ef-

fects—more marked in the case of the male than in the female. Only 50% of all the matings resulted in living offspring. Of 100 full term litters born of alcoholic parents, 18% were still-born and 46% of the individuals in the living litters died very soon after birth. Of 194 matings of the first generation from alcoholized parents, 55 gave negative results or early abortions occurred; there were 18 still-born litters totalling 41 young, and of these 17% were deformed. Of 121 living litters, together totalling 199 young, 94 died within a few days after birth and of these 15% were deformed; of the 105 that survived, 7% showed deformities of the eyes. It is interesting to observe that of 126 controls of the same stock, not one of the young was deformed at the time of birth.

The records of the matings of the second generation are still worse, there having been higher mortality and more pronounced deformities, while the few individuals of the third generation which survived were generally weak and in many instances sterile, even though paired with vigorous and prolific normal mates.

It is of extreme interest to note that the structural defects shown by the descendants of alcoholized animals seem to be chiefly confined to the central nervous system and special sense organs. Many of the young animals show gross tremors, paralysis agitans, and paralyses of one or more legs. The quality of individuals from the same parentage varies inversely with the size of the litters in which they occur.

It is noteworthy that inbreeding added to alcoholic poisoning produces a much worse condition in the offspring than can be brought about by either alone.

It is quite remarkable and of extreme interest to call attention to the fact that these writers show that the female offspring from alcoholic males are less vigorous and more frequently deformed than the male offspring. Furthermore, the progeny of heterogeneous matings of such male and female offspring further emphasizes an inferiority in other particulars on the part of the female offspring of treated males. On the other hand the male offspring from alcoholic females are inferior in quality to the female offspring, and heterogeneous matings of such male and female offspring further prove the inferiority on the part of the male offspring from treated mothers. It is of interest to note that these results reverse the statistical data obtained by Calderini (2) and Boudin, both of whom have observed that pellagra is more apt to be transmitted from father to son and mother to daughter than the reverse.

We find then that the results of clinical statistics in the old world show the extreme frequency of the transmission of pellagra from parent to offspring, and the most interesting experiments of Stockard and Papanicolaou clearly indicate the hitherto imperfectly recognized but very extraordinary influence that chronic intoxications exert on heredity. *When we take these facts in connection with the undoubted common occurrence of pellagra without the usual classic symptoms, we seem to be in a position readily to answer all of the*

more important objections that have been urged against the supposed relationship of maize intoxication to the disease under discussion.

It becomes perfectly plain why a man may eat maize throughout his life without experiencing any particular effect, while at the same time he may transmit degenerative changes to his descendants, which become more and more marked as one generation follows another.

We readily understand why whole communities may likewise make maize a basis for their dietary, and still go on for a long time without pellagra appearing.

It likewise becomes clear why an individual may be pellagrous, notwithstanding the fact that neither he, nor possibly even his immediate ancestors, have ever eaten this cereal.

We have no difficulty in understanding how it is possible for the poisons of Indian corn to be taken in for generation after generation, with a slowly cumulative effect; for a long time there might exist only a mild degree of intoxication, the affected individuals probably presenting few evidences of disease, or where the poisoning is more intense, showing what is called *pellagra sine pellagra.* It is thus possible that only after this has gone on for two, three, four, or even more generations, will the intoxication ultimately terminate in a development of all of the phenomena characteristic of classic pellagra—the outbreak being comparable to delirium tremens in very chronic alcoholism.

The only class of cases which present any difficulty, in the light of the foregoing theory, are those instances of alleged pellagra that have occurred in non-maize-eating districts, and where, as a consequence, it is presumed that none of the ancestors of the affected persons have eaten maize. However, if the reader will look over the chapters in this treatise devoted to a consideration of what is called "parapellagra," the author thinks he could hardly fail to admit that there is in most and possibly all of these cases a very grave doubt as to their being pellagra. Certainly in a great proportion of instances they were actually shown to be something else, while in most of the remaining cases the symptoms were of such a nature that the matter is clearly in doubt.

Finally we should not forget that the same moulds growing on other starches than those of maize produce beyond question similar poisons, which readily offers an explanation of possible cases of genuine sporadic pellagra which might conceivably have their origin in the long-continued use for several generations of food products prepared from badly conserved cereals.

While the author is inclined to the belief that pellagra is in the main caused by the mould toxines of maize he wishes to state distinctly that he also thinks that other deleterious agencies which are incident to the use of maize as a food play a subordinate rôle; such agencies are the albumenous substance called zein, as well as certain ferments that occur in Indian corn, all of which are toxic; likewise, it is certain that the proteids of this cereal do not contain all of the amino-acids necessary for nutrition, and that they are not perfectly digestible;

when it is finally remembered that foods prepared from maize are rarely or never properly cooked, and that in many parts of the world the unfortunate peasants have throughout life little or nothing else to eat, it is not difficult to understand that all such influences combined might well have an important bearing on the causation of this malady. Indeed, there is reason for the belief that they may quite independently of mould poisons produce a high degree of degeneration in those who are habitually subjected to their evil effects, as in well shown in the maize-eaters of the tropics, where the constant high temperature prevents the formation of the mould toxines; under such circumstances, however, it appears not unlikely that the acute symptoms of this disease either do not occur, or are rare. Can it be then that the inherent bad properties of maize play the dominent rôle in this affection, and that the mould toxines act only in a subsidiary manner, possibly predisposing in the spring and autumn, at which time they are only formed in temperate climates, to the acute outbreaks of classic pellagra? Certainly we are not in a position to deny the possibility, or even the probability. We can only say that inasmuch as both the natural and artificial poisons of this cereal are almost always more or less combined in foods made from it, that there is good reason for affirming that it is extremely probable that they constitute the pathogenic agencies that cause pellagra. Concisely stated the chief reasons for this assumption are as follows:

(1) *It may be affirmed as a fact that pellagra existed in no country before the introduction of maize as a food.*

(2) *That there exists no records that show that this disease made its appearance in any place until this cereal had been used commonly as a food for approximately two or more generations.*

(3) *That following the introduction of Indian corn into France pellagra became common in those provinces where it was usually eaten; about the middle of the last century, owing to the teachings of the French pellagrologists, maize was abandoned as a food for man, and pellagra gradually disappeared,—the last case having been reported in 1902.*

(4) *Pellagra has nowhere occurred in its endemic form except in those places where Indian corn is or has been consumed as a food by man, and, with the possible exception of the tropics, this grain has been nowhere eaten where pellagra did not sooner or later appear. Even in the tropics the consumers of maize show a high degree of degeneration.*

(5) *If maize produces pellagra this result must be the consequence of an intoxication.*

(6) *We know that one of the constituents of maize is a tox-albumen—zein—and that it also contains poisonous ferments, and that it is possibly poor in the so-called vitamines; furthermore, in practically all instances where it is used as a food in spring or autumn it contains mould toxines (phenols).*

(7) *In the amounts usually taken these poisons produce little or no immediate effect, but it seems wholly probable that their use*

throughout life, and from generation to generation, must be followed by evil consequences.

(8) *It is certain that chronic intoxications are highly hereditary.*

(9) *It is known that in about 50 per cent. of cases those who have pellagra are the offspring of parents one or the other, or both of whom have had the classic symptoms of this disease.*

(10) *As pellagra frequently occurs without any of the classic symptoms is it not possible that many, or even all, of the remaining 50 per cent. of its victims are the progeny of those who are afflicted with this mild form of the malady? According to the author's hypothesis this is assumed to be true, and therefore pellagra in practically all cases is thought to be hereditary.*

(11) *This view is greatly strengthened by the fact that all pratical pellagrologists of the old world—where clinical data on this disease have been collected for nearly two centuries—unanimously hold that pellagra always lasts throughout life,—it being in truth the most chronic and intractable of all diseases.*

Of course the author refers in the above to the endemic form of pellagra which occurs in maize-eating districts, and has no reference to those rare cases which are sometimes seen where this cereal is not used as a food, and which he has ventured to call "parapellagra."

The foregoing is all the more to be considered seriously as there are apparently insuperable objections to all other hypotheses so far advanced in explanation of the causation of pellagra. Of these only two have secured any considerable number of adherents, these being the theory of *protein inanition,* and that of *infection,*—both being among the oldest and most discussed of the many conjectures indulged in by the earlier authors who wrote on this subject.

Among the cheif objections to the former are that the peoples of several countries have for ages lived and thrived on a dietary of cereals containing probably even less of all nurtitive elements than that furnished by maize to the Italian and Roumanian peasants, that modern investigation shows that the human being flourishes on even less albumens than were given to the subjects recently used in experiments carried out to prove this hypothesis, that people, especially in the United States, have pellagra notwithstanding that a large proportion has always had an abundance of good foods, and that in starvation we encounter neither the symptoms nor the pathologic changes usually exhibited by pellagrins.

The theory of infection can hardly be true in as much as no one has shown—notwithstanding innumerable attempts to do so—that there is any organism constantly associated with pellagra, and for the reasons that the disease is not contagious nor can it be conveyed by inocculation, that it is more highly hereditary than any infectious disease, and that neither in its pathologic alterations nor in its more characteristic symptoms does it resemble any of the known affections of this character.

In the light of the foregoing discussion the author then would tentatively and with the greatest diffidence offer the following formula as a definition of our present knowledge of the etiology of pellagra:

Pellagra is an extremely chronic endemic affection of temperate and subtropical countries—i. e., where Indian corn is grown and much eaten. While the malady has been generally thought in the past to be the consequence of inanition, the result of an inadequate diet, it has been more recently regarded as the effect of the habitual consumption of Indian corn, and possibly in rare instances of eating other starchy foods that have been acted upon by low vegetable forms; if this theory should be found to be correct the disease is probably more directly the result of the action of certain phenol poisons, produced by moulds while growing in these cereals, and possibly of albuminous and ferment toxines contained in sound maize, all of which together, acting from one generation to another, and not unlikely intensified by bad hygienic conditions and insufficient and imperfect food, ultimately culminate in a frank outbreak of the classical symptoms of this disease. Finally, it can not be too strongly urged that the malady is probably always hereditary, no person ever in his lifetime eating enough maize to produce the disease.

Answer to the Objections Against the Mouldy-Maize Theory of the Causation of Pellagra.

There has been opposition to the maize theory of the causation of pellagra from the time that the idea was first seriously propounded by Fanzago in 1807, though it is a notable fact that no pellagrologist who has made a serious study of this matter has wholly repudiated this view. Irrespective of a few French writers, such as Bouchard, Boudin, and Landouzy, who had had little or no experience with endemic pellagra, and who were the slaves of their belief that this disease may occur without eating maize, it can hardly be said that any writer or investigator of eminence has combatted in its entirety the maize doctrine of its causation. The only European pellagrologists of note who have failed to accept fully this idea were Morelli, Lussana, Frua, and Gemma, four extremely capable investigators, who did their work and added much to our knowledge of pellagra during the two or three decades that followed the middle of the last century. All of these observers attempted to determine whether or not poisons are produced by microörganisms in maize, and notwithstanding that it was admitted that there were reasons for the belief that this occurs, they were all so obsessed with the idea that pellagra is an acute process, and should instantly follow on the administration of the toxic substances believed to produce it, that they naturally ranged themselves with the opposition when it was found that this did not occur. It is, however, well to remember that these remarkable investigators were for practical purposes believers in the close relationship of maize to pellagra, since one and all they advocated the view that this cereal is an insufficient food, and that pellagra, being a disease of inanition, is in the great majority of instances caused by the Italian peasantry

attempting to live upon it exclusively. The only opposition then to the maize theory that emanated from capable and scientific sources of that period was that of investigators—consisting in the main of the four just mentioned—who, while believing that maize is associated with the production of pellagra on account of its being a bad food, could not find satisfying evidence of the view that low vegetable forms so alter this cereal as to cause it to become toxic, or that they produce poisons in it which are to be looked upon as the real pellagrogenic agencies.

Notwithstanding that there has never been complete agreement as to the causal relationship of maize to pellagra, the opposition did not really become active until some little time after the publication of Balardini's classical work in 1845—and was in the main due to the failure of the investigators just mentioned, and a few others, to produce toxic symptoms in animals with bad maize products, and to the discovery of what was supposed to be pellagra in persons who had never eaten maize. The former objection bore with considerable force on the subject until later investigation definitely determined that the principal, if not the only, poisons in bad maize result from the life activities of the hyphomycetes, and the demonstration that these plants vary widely in their capacity to produce toxic substances. Discordant results were largely due to the fact that many of the experimenters of the last century operated with artificially decomposed maize, subjecting the culture during its growth to conditions that are now known to be inimical to the production of the mould poisons; indeed, it may be confidently asserted that many of the earlier experiments could not apply with any force to a solution of this question, inasmuch as the conditions under which the fermentation was brought about favored the development only of the schizomycetes, and resulted in the putrefaction rather than the somewhat analogous but really different processes that occur when moulds attack this cereal. As it is quite certain that bacteria play a wholly unimportant rôle in the changes that ordinarily occur in bad maize, it is at once evident that the results attained by the use of artificially decomposed Indian corn have no important bearing on this question.

Those who are interested in these negative results are referred to the various papers of Lussana (1, 2), the report of the commission consisting of Biffi, Todeschini, Valsuani and Zucchi, the investigations of Gemma (6, 7), Bellini, Monselise, and others.

The second objection is of decidedly greater importance than the first, for if it can be conclusively shown that pellagra may occur without any connection with maize products, the theory would, of course, have to be abandoned. This objection, therefore, deserves the most careful consideration of the investigator, as upon its refutation depends the whole modern conception of the malady under discussion.

Very early we find cases of supposed pellagra reported in districts where maize eating, to say the least, was very uncommon, and

where all of the facts tended to show that there could be no possible relationship between this cereal and the disease from which the patients were suffering. Thus we find a case of this kind, from New Castile, was observed by Thierry in 1753 (published, 1755), three cases were reported by Careno, of Vienna, in 1794, and others in 1842 by Roussel, from central France, by Brandis, from Westphalia, by Hameau (fils), from Africa, and at a later time alleged examples of this affection by various French writers. Bouchard considers the case reported by Theopile Roussel, in 1842, as being the first example of sporadic pellagra which has been sufficiently well described to make it clear that it was not some other malady, though subsequently the celebrated pellagrologist who reported the case felt very doubtful as to the diagnosis. At a somewhat later period the exact status of such cases created a great diversity of opinion in France, and culminated in a discussion that lasted many years. The results were, however, not of sufficient importance to necessitate their being considered at length in this connection, it being sufficient to say that Landouzy wrote a brochure on the subject in 1850, and called his cases "Sporadic Pellagra"; that two years later Bouchard (2) published a somewhat larger book, in which he sustained the views of Landouzy; that in 1865 a ponderous volume was written by Billod (2) on a disease observed in France among the inmates of the various asylums for the mentally weak, which this writer called the "Pellagra of the Insane." Rather curiously, after the observations referred to, these various pellagra-like affections seem to have gradually disappeared in France, so that instances of the kind were only reported at great intervals until within the last few years.

Still more recently as already mentioned this pellagra without maize has been revived in England by Sambon and Chalmers, Hammond, Box, and others. As Sambon has been very strenuous in the advocacy of his views, he has stirred up in England, and also in the United States, a considerable opposition to the maize theory; naturally this has been followed by reports of several cases of "pellagra," without maize, both here and in England. Such is, in brief, the history up to the present time of a class of cases, which, since they bear some resemblance to genuine pellagra, the author has ventured provisionally to call *parapellagra.* Doubt having thus been raised as to the maize theory of the causation of pellagra, other objections were in due course brought forward, the principal ones of which will now be categorically considered.

The arguments employed by the opponents of the maize theory are always the same, and have served as their stock in trade for the last half century. Nowhere are they stated more clearly or with greater force than by Lussana (1).

(1) This able investigator, after having shown that the *Sporosorium maydis,* of Balardini, occurred both in America and Europe, very properly assumed that it should produce in maize the poison of pellagra in both countries if it were, indeed, the cause of the

malady; at that time, however, pellagra was not known in the new world, and Lussana argued that the parasite just described could, therefore, have nothing to do with the disease.

(2) He insisted that where a toxic substance is placed in the food it affects everyone alike, and he asked if bad maize be the cause of pellagra, why it is that all who partake of it do not suffer?

(3) He inquires what sort of maize poisoning is that which is of such curious character that it respects the affluent and well-nourished, and strikes exclusively the very poor, and has a predilection for one or two persons only of a family?

(4) And why, if the trouble be due to a poison, is it that the disease is never relieved when it has once attacked its victim, as he knows of no toxic substance that continues to act longer than it remains in the organism?

(5) What kind of poison is it that has the curious idiosyncrasy that it is conveyed by heredity from one generation to another, but cannot be communicated by the milk of the victim?

(6) Finally, that writer thinks the argument is at an end when he recounts the fact, already discussed, that a disease exists, which he believes is genuine pellagra, without the victim ever having consumed maize products.

Before categorically answering the foregoing we must again refer to the fact that it is perfectly well established that pellagra did not appear in Europe until maize became the staple food of the communities where the disease has since raged; that the introduction of this cereal was invariably followed after a period of some years by the appearance of the malady; that other peoples who do not consume maize live under precisely similar conditions, and even in the same communities, and yet do not have pellagra, as is well shown in Roumania.

Of the greatest importance in this connection is the undoubted fact that pellagra appeared in France a generation or so after maize came into general use as a food, and that it subsequently disappeared when this cereal was no longer employed as a common aliment by the human being. According to Arthaud, the chairman of a committee to investigate this subject, pellagra first appeared in southwestern France about 1750, but certainly did not become at all common until about 1825; the disease gradually increased until about the middle of the century, when it was exceedingly common. In a very short time it was generally recognized that this affection had some connection with maize, and under the powerful leadership of Roussel, Costellat, Tardieu, and others, knowledge of this fact was thoroughly disseminated among the people, and as a consequence this cereal was gradually abandoned as a food, until at the present day it is no longer used for this purpose to any extent in France.

Being unable, as before mentioned, to obtain from other sources satisfactory information as to the present consumption of Indian corn in France, the author wrote to his Excellency, Jules Jusserand, French

Ambassador to the United States, who most kindly replied that this cereal is no longer used in his country as food for the human being.

Along with the decline of the use of Indian corn as a food, pellagra became less and less frequent, the last case known in France having been, according to Regis, dismissed from the asylum of d'Auch in 1895. Certainly no one could desire more striking proof of the relationship of maize to pellagra than is shown by the history of this disease in France.

We will now discuss the objections urged by Lussana in the order in which they are outlined on the preceding page.

(1). It was objected that pellagra does not occur in America notwithstanding that this cereal is there much eaten, and that the organism which is thought to render it unfit for use is unquestionably there present. The recent discovery of pellagra in the United States of course nullifies this argument against the theory; it may also be remarked that Babcock (4) has shown that there are grounds for the belief that the disease has existed in South Carolina for at least three-quarters of a century, though the proof is not conclusive.

In this connection attention may be called to the fact that it has been recently asserted by Pieracchini that pellagra probably does not exist in Brazil, notwithstanding that there maize is much eaten. Unfortunately we are not at present in a position to determine this matter with certainty, but it may be well doubted as to whether this author's conclusions are well-founded. As he only visited some of the larger towns, it can hardly be assumed that he came in contact with representative examples of the maize-eating Brazilian of the country districts, since it is quite probable that many of those living in the centers of population are either immigrants from Europe, or the children, or at most the grandchildren, of ancestors coming from the old world. Certainly the conditions pictured by this writer in no way correspond with the description given by Savage-Landor of the miserable peasantry of the interior of this great country; in his pages there is a strong suggestion of the pathetic account of the pellagrous population of Northern Italy given by Lombroso in the opening chapter of his well-known treatise on this terrible disease. Moreover, attention may be called to the fact that nowhere in the tropics is there the frank development of pellagra such as occurs in colder latitudes, and that it is therefore not surprising that this traveler makes no mention of typical examples of this malady, but his account of the profound degeneration exhibited by the miserable maize-eating Brazilian agriculturists has its only parallel in the description given by various writers of the unfortunate Italian and Rumanian peasantry, whose ancestors have for generations lived on Indian corn. (Vol. I. pp. 64 and 315). At this point mention may be made of the fact that Ceni (11) and Gosio (8) have both shown that the toxins elaborated by moulds are only produced in appreciable quantities at ordinary temperatures—the optimom bring about 77° F.—and no better proof of the truth of the mouldy maize theory could be desired than the failure of the disease to develop in maize-eating countries where there is a fairly constant higher temperature. It has even been shown by

Tiriboschi (2) that the moulds die when kept for some weeks at 98.6° F.

Finally, it should never be forgotten—whatever may be the fate of the author's speculations as to the causation of pellagra—that the records clearly show that there is never an outbreak of the malady until maize has been the common food of a community for at least two or more generations.

(2) In reply to the assumption that all persons should suffer alike who partake of a poison it may in truth be urged that this is by no means always the case; the effects that will result depend largely on the strength of the toxic substance, since where its virulence is not great, or where it is in only small amount, many will escape with little or no ill consequences; the results are, likewise, dependant on the susceptibility of those to whom the poison is given. It is well known that those who are physically strong are able habitually to tolerate quantities of such nerve poisons as alcohol, cocaine, morphine, etc., as would be the inevitable death of weaker persons, even were they to attempt to emulate their more vigorous neighbors for a single day. It is therefore not strange that it is the weak and dyspeptic who preëminently have pellagra, thus lending clinical support to the theories of Neusser and DeGiaxa, already referred to.

In this connection attention should be directed to the fact that it is by no means certain that those maize eaters who escape frank and obvious manifestations of pellagra suffer no ill consequences as a result. In truth, our knowledge of the subject would seem to warrant the conclusion that perhaps all of them are more or less affected by the poison, though the organic lesions produced may be of such mild character as not to be followed by unmistakable symptoms, and it is quite likely that the children of such subjects, particularly where they also eat maize, early develop the dyspeptic tendencies which so often in later life culminate in this dreadful disease. Unquestionably it is such unfortunate individuals as these who in later years become pellagrous when placed under unfavorable conditions of life.

(3) The statement that the well-nourished never have pellagra is erroneous, though undoubtedly true in the vast majority of cases. Even Strambio speaks of the fact that after death the bodies of pellagrins sometimes appear in very good condition (2, §9), and arffims that it is not true that the well-to-do always escape the disease (1, §51). As a matter of fact in America a very large proportion of the pellagrous population belongs to the middle classes, and the malady is frequently observed in people who have had abundance of all kinds of foods throughout their entire lives. The assumption that only the miserably poor have the disease is common among European writers, but its occurrence in this country in all classes but shows again how dangerous generalizations are unless every fact is accurately known. The occurrence of this affection only in the poorest people of Europe and in practically all classes in the southern portions of the United States is absolutely in keeping with the maize theory of its origin, since in the old world this grain is only eaten to any considerable ex-

tent by the peasants, while in America it forms the staple bread of many well-to-do people, and in one form or other is largely eaten by everybody in the south. In the northeastern portions of the United States, on the other hand, where but little maize is consumed, pellagra is extremely rare, and it is probable that even those cases reported as originating there belong in the parapellagra group.

The fact that pellagra has only recently become common in America may be readily explained when we remember that our people have never eaten maize exclusively, and that almost everybody has always had an abundanc of meats and other wholesome foods; under such circumstances we would naturally expect that the development of the disease should likely be greatly delayed. For the same reason it is quite probable that only such persons as have severe and far-advanced lesions will show the external manifestations,—thus accounting for the greater tendency to a fatal termination in American pellagrins.

(4) As regards the tendency of pellagrins gradually to grow worse, there can be no question, and the author is fully in accord with Strambio, Verga, Lussana, and Fritz in the belief that its victims never fully recover. That this is the result of the poison remaining in the system is, of course, too improbable even for discussion, but it is undoubtedly true that our knowledge of the morbid changes in the body shows clearly that many of them are of such character that when once produced the parts never return to a normal condition; such changes are some of those that are found in the skin, and those in the bones, in the blood vessels, in the sympathetic nervous system, in the spinal ganglia, and in the brain and cord. With such an array of permanent lesions it can be no wonder that the bodily functions are carried on badly and that the victim often has a recurrence of symptoms on the slightest lowering of the general vitality. The presence of these grave alterations in most of the vital organs adequately explains many of the chief objections which have been urged against the maize etiologic doctrine of this malady.

(5) Lussana urges against the toxic theory of the causation of pellagra that the disease is unquestionably hereditary, and, in view of this obvious fact, thinks it doubly strange that the poison is not excreted by the mammary glands. However, such objections have today but little value. As shown in the preceding chapter, where parents have been under the influence of poisons at the time of the birth of their progeny, the latter often suffer from all the symptoms exhibited by the former, and, in addition, show pronounced evidences of what is called "degeneration." As also shown by a series of brilliant experiments, recently reported by Stockard and Papanicolaou, intoxicants may fail to produce any sort of pathologic alteration in animals, but when these are bred, even to other animals that have not been subjected to such influences, they frequently abort, and even when their offspring are born alive about one-half die while young, and of those that survive a large percentage are deformed; the results in the third generation are even more disastrous,—there being a still greater numbr of miscarriages, more frequent deformaties, general weakness, sterility, etc. (For further data the reader is referred to the chapter on

etiology.) Indeed, it would appear from recent investigations that not only are toxic processes highly hereditary, but that they are the only pathologic states that can be regarded as commonly exhibiting such tendencies.

Though denied by Gemma (2), Lussana, as before mentioned, came to the conclusion, as the result of a few observations, that the poison that produces pellagra is not excreted with the mothers milk, but, even if this be accepted as true, it would not necessarily clash with the facts just recited respecting heredity. Since the intoxication, whatever it may be, is unquestionably of a most chronic character no one could expect that enough of the poison could be excreted during the comparatively short period of lactation to produce the disease in the infant. On the whole it would seem more probable that such influences play little part in the transference of toxic processes, and that we are rather to look for an explanation of such occurrences to imperfections in the germinal cells, and to faulty nutrition during fetal life. Likewise, we should not forget that from infancy onward the offspring of such parents are more than apt to be constantly exposed to all the detrimental factors that have wrecked the physical well-being of their forbears.

(6) Lastly we will consider those cases of pellagroid character, unassociated with maize, which have been called "sporadic-pellagra," the "pellagra of the insane," and "peudo-pellegra." To begin with, it should be observed that it is certain that many of the cases reported as such could not be regarded as belonging in this category. It is admitted by Bouchard (1), who is one of the strongest advocates of the view that the parapellagras may occur independently of maize, that none of the instances of this kind are well authenticated prior to the case reported by Roussel in 1842, and regarding the true character of which the latter author was subsequently much in doubt. It is equally clear that many of the cases later reported by Billod (1, 2) and Landouzy (1, 2) are of such uncertain character that it is impossible to determine from the clinical data given as to whether the patients had true pellagra. The appearance together of diarrhoea and some redness of the skin is by no means a sufficient warrant for a diagnosis of this complex disease, and excepting those instances where it is possible to determine the exact nature of the dermal alteration, as well as the character of the other clinical phenomena, the diagnosis must in all cases remain a matter of great uncertainty. In the insane—and it was among such cases only that Billod labored—the author has no hesitation in saying that in a great majority of cases a diagnosis from clinical symptoms is impossible, unless there is a perfectly clear history of the nervous symptoms that came on before the mental changes occurred, and, as such accurate histories probably exist in none of the cases that have been reported, their true nature must always remain a matter of doubt. It is well-known that diarrhoea and cutaneous manifestations are frequent in the insane, perhaps for the same reason that they are common in pellagra,—both in many cases doubtless depending on altered innervation; it should also not be forgotten that under such circumstances the

skin is exceedingly sensitive to irritants, particularly light, and it is doubtless true that many of the instances of so-called pellagra of the insane were simply sunburn. It is furthermore well-known that a number of the cases of so-called "pellagra of the insane" reported by Billod were found on examination by competent dermatologists to be simply parasitic skin affections, with no sort of possible relationship to this disease. During the midst of the discussion that raged about the middle of the last century Billod exhibited three of his cases from the insane asylum at Sainte-Gemmes at the Paris Academy as representative instances of an alleged epidemic of pellagra that was at that time in progress in the institution referred to. The dermatologist Gibert, on a somewhat casual inspection, was inclined to regard these cases as sunburn, but Cramoisy and Pourquet perceiving broken hairs on the faces of the patients, made a microscopic examination, and demonstrated that the lesions were due to the *trycophyton.* (See Roussel, 3, p. 626.) On one occasion the cases at the asylum mentioned, as well as those of the similar institution at Auxerre, were found by Bazin to be in every instance barber's ringworm.

Unfortunately as yet, even after death, there is ordinarily no way of determining the matter with certainty, but if we may accept the findings of Carmao in France, and Mott in England, it seems extremely likely that the pathologic changes in these parapellagras differ in important particulars from the alterations that occur in the endemic disease.

The parapellagras described by Landouzy, Bouchard, and others in France, as well as those cases more recently reported by Sambon and his followers in England, rarely impress one, from the descriptions given, as being identical with the pellagra common in maize-eating districts. The pellagra-like details of such cases appear to be forced in the great majority of instances, and a very pronounced impression is given that the symptoms do not in every way coincide with those of the genuine disease, and that a thorough examination by a competent pellagrologist would have dispelled in all likelihood the probable error. These remarks are not made in a spirit of captious criticism, but are simply the statement of the impression made on the author by a careful perusal of the clinical histories of many of these cases. It should not be forgotten furthermore that no experienced pellagrologist has had an opportunity—so far as the records go—of passing on any of these cases, and that practically without exception the literature on the subject is from the pens of writers who had no great practical acquaintance with genuine pellagra, in fact, usually none at all, and that in most instances they were unquestionably influenced by a strong desire to prove a preconceived theory.

While it then may well be doubted that the parapellagras are identical with the genuine disease, attention may be called to the fact that according to the present conception of the etiology of the latter affection there is no reason, *a prior*, why morbid states, closely related if not identical, may not occur in those who have never eaten maize products. It is well-known that the same moulds that produce toxines in maize are likewise capable of forming apparently similar poison-

ous substances in chestnuts, wheat, and other starchy foods, and that the reason that maize is more commonly attacked is that the physical conformation of the seed is such as to render it exceedingly susceptible to the invasion of micro-organisms. We can, therefore, easily understand why the poor, particularly those with dyspeptic tendencies, with weak powers of resistance, living from generation to generation under unhygienic conditions, and being depressed by the use of alcoholics, or suffering from chronic diseases of any kind, might very readily develop lesions in the central nervous system and blood vessels as the resultof the constant consumption of breads made even from fairly good wheat or other cereeals, since it is highly probable that practically all of them after being ground into flour, if not before, are more or less attacked by the hypomycetes; of course the condition becomes infinitely worse if such an individual should habitually eat breads made from flours that are old, or held in receptacles that are seldom cleaned, and which are kept in damp, ill-ventilated pantries.

The disagreements in symptomatology between the pellagra of the maize-eating districts and the parapellagra of other parts of the world is precisely what might be expected as the consequence of the probable differences between the poisons, or, more likely, variations in the proportions and amounts of such substances that are produced in maize and those that are formed in other starchy food.

While it is of course recognized that, although their opinion cannot be offered as positive evidence of the truth or falsity of any theory of the causation of pellagra, it must be admitted that where the best scientific men of those countries where this disease has pervailed for a century and a half and has been most studied accept with practical unanimity the maize doctrine of its etiology, their views are entitled to the highest consideration. Observations extending over such a period ultimately assume the value usually attached to the results of laboratory experiments, and become proof of exceptional importance,—as is recognized in many instances where ideas as to etiology are based simply on long clinical experience. That on the one hand this is the attitude of the foremost workers on this subject in Italy, Austria and Roumania, which includes some of the greatest names of contemporary medicine—a perusal of current medical literature will show, while on the other there is hardly a writer of these countries whose name is known beyond the borders of the town in which he lives who rejects this view. Indeed, it may be said that Tizzoni, who has discovered what he believes to be the bacillus of pellagra, is the only investigator of European reputation who has within the last decade or two denied the causal relationship of Indian corn to this terrible disease. For the sake of the convenience of those who might be interested, it has been thought advisable to append at this point a list of the more prominent workers who are advocates of this theory.

In Austro-Hungary we have Merk, Niederman, Konrad, Farkas, Veress, Horbaczewski, Raubitschek, Ballner, Hausmann, and Hirschfelder.

In Roumania we have the well-known Babes, who has devoted a great deal of attention to this subject, Sion, Manicatide, and Procopiu.

In Egypt we have Sandwith, Warnock and Pearson.

While in France pellagra no longer exists, we still have the subject occasionally considered by French authors, among whom the most prominent are Marie, and Poussie, both of whom are advocates of the mouldy maize theory.

In Russia the disease only occurs to a limited extent, but we have in Kozowsky an ardent advocate of the maize theory, and at the same time one of the foremost living writers on the subject of pellagra.

In Germany the only writer on pellagra of any importance at all is Tuczek, who is a strong advocate of the mouldy maize theory.

In Italy we have adherants of this view first and foremost Gosio, who has done more to put the mouldy maize theory on a solid basis than all others combined; there are, in addition, Majocchi, Finzi, Agostini, Devoto, Ferrati, Antonini, DiPietro, Bassi, Ceni, Besta, Gavina, Rizzi, Peglion, Terni, Tiraboschi, Ghirardini, Palladino, Sanarelli, Tanzi, Audinino, Colloidi, Camurri, Lui, Cazzamolli, Zuccari, Mariani, D'Abundo, Vedrani, Moreschi, Carletti, D'Ormea, Obici, Bonon, Rossi, Zanon, Alpago-Novello, Pianetta, Ziveri, Mannini, Tambroni, Ricci, Valtorta, Righetti, Brugnola, Bravetta, and many others.

THEORY OF PELLAGROGENIC TOXINES IN OTHER STARCHES.

The possibility of the same micro-organism producing similar poisons in other starchy substances than that of maize was long ago recognized by Montesanto and later by Bouchardat and subsequently advocated by Tardieu. More recently Lombroso (7) made a number of experiments that confirm this idea, as did also Lussana and Chiotto.

Some investigators have worked with pure cultures of different species of moulds, and have shown that as a result of their life activities poisons quite similar or identical with those that are produced in maize by these organisms are also elaborated by them when developing in other starches and in sugars. This subject has been particularly studied by Gosio (1).

It was later shown by Peglion that these moulds develop in chestnuts, with the production of substances that give Gosio's reaction. This is a matter of much importance, as in some parts of northern Italy chestnuts form a very considerable part of the dietary of the peasant class, particularly in the winter.

Still later it was shown by Ceni (22) that cheese contains mould toxines that are poisonous to dogs, and in another paper confirms the fact that the poisonous substances are produced when hyphomycetes develop in wheaten starch (23).

CAUSATION OF LOCAL SYMPTOMS.

Causation of skin symptoms.

The most striking and characteristic symptoms of pellagra are caused by the well-known skin lesions, which resemble ordinary sun-

burn so closely that there is little wonder, when we consider the imperfect development of scientific medicine at that period, that Frapolli, the earliest Italian writer on this subject, should have decided that this disease is nothing more than a peculiar and unusual manifestation of insolation, nor that this view should have been sustained by such respectable writers as Albera, Nardi and Brugnoni. That there in, indeed, some direct connection between the action of the sun's rays and the pellagraderms was first made evident by the experiments of the distinguished pellagrologist Gherardini, who records in his masterly brochure on this subject a direct demonstration of the truth of this view. He says:

"I was able to witness this action of the sun on certain pellagrins in our hospital, who had permission from their physicians to go wherever they pleased. By means of small gifts and by persuasion I succeeded in getting a number of these patients to sit day after day for several hours with always the same part of the body exposed to the direct action of the June sun. After some days it was found, somewhat to my embarrassment and still more to theirs, that the parts had become red and shining, some being swollen and others not, the same being accompanied by a feeling of discomfort and a burning and itching; finally they became weak, the skin of their faces reddened, and they complained of vertigo" (pp. 41-42).

The foregoing experiments were carried out on ten patients, the writer stating that he took care to expose those parts of the skin which showed lesions on the patient's entrance to the hospital. One might be disposed to think that the exposure to the sun was such that it would have produced reddening of the skin in normal individuals, but it is certainly singular that the patients should have at the same time developed the other typical symptoms of a pellagrous attack. Gherardini, however, was perfectly aware of the fact that pellagra is not simply an insolation, and distinctly states that the skin symptoms are nothing more than an external manifestation of a general malady (p. 40).

The experiments just referred to were repeated by Strambio (4) "an infinite number of times." He says that the skin lesions occupied solely the exposed surfaces, with the exception that the palms of the hands are never diseased, and that the face is only rarely attacked (pp. 9-10).

At a later time Perroud discussed with great acumen the action of the sun in producing pellagraderms. He declared that neither the luminous nor heat rays were responsible for the lesions, and after an argument remarkably well sustained concludes that this result is due to the chemical rays of the sun.

Subsequently Bouchard (4) made some experiments in this connection and decided that the violent rays of the spectrum are the ones that are responsible for the effects produced. By covering a part of the arm of a pellagrous patient with diachylon ointment and leaving a spot in the center bare he showed that only the unprotected areas developed the erythema, and concludes that unquestionably the lesions are the result of the sun's action.

The most instructive and interesting paper which has ever appeared on the skin lesions of pellagra was written by Raymond, who in addition to a remarkable clinical description observes that while it is evident that the sunlight plays a part in the production of pellagraderms it is equally clear that this is not the sole cause. The whole course of the disease shows that where the sun apparently produces effects of this kind it is as a consequence of the weakened condition of the tissues, which are diseased as a consequence of the pellagrous process.

Clinical experience also points to a connection between the sun's rays and the pellagraderms, as is shown by Vales, who says in his excellent monograph on pellagra in Yucatan that the erythema frequently occurs on the backs of the feet of the Indians as a result of the fact, he believes, that they seldom wear shoes; he likewise notes that the eruption on the faces of the women is much less frequent than in men, a clinical feature which he thinks is the consequence of their wearing large bonnets. Of like significance is the case referred to by Neusser (1) where the lesion appeared on the palmar surface of the hands in a pellagrin who was accustomed to walk in the open with his hands crossed behind his back. Gemma also notes that in Italy the lesion in women begins on the legs at the bottom of the petticoat, and in men at the ends of the trousers; a similar connection between the clothing and the lesion is noted on the arms. It is, however, evident that the hands, feet and face are the sites of predilection, as is shown by the observation of Neusser in Roumania, where it was noted that gypsy children, though going stark naked, developed erythemas only in these situations when they were attacked by pellagra.

Maize toxines have some causal connection with skin lesions according to the observation of Di Pietro (6), who, during the course of some immunization experiments on rabbits, observed that they developed symmetrical erythema, with loss of hair, three or four months after a systematic course of injections of this poison was begun; the writer was careful to exclude mange and other zymotic diseases which might possibly have produced this result. In this connection it is of interest to note that Gosio (7) calls attention to the fact that in chronic poisoning by phenols eczematous skin eruptions are common—there thus being a striking similarity between their action and that of the agencies that produce pellagra.

It is likewise the experience of the author that pellagraderms frequently have their origin in exposure to the sun, it being an exceedingly common occurrence for intelligent patients to assert positively that their trouble began in this way—this particularly occurring in those who do not habitually labor in the fields, but who suddenly emerge from the confinement of the winter, and engage in outdoor work. Even after a few hours exposure, particularly in the spring, pellagrous patients often develop the erythema, and strange to say, this is almost invariably quickly followed by the other constitutional symptoms of the disease. It is likely, as the experiments of Gosio would seem to indicate, that toxines are produced in the body as a result of the skin lesions, and it is also probable that the resistance

of these patients is so lowered that the slightest disturbance is followed by the development of symptoms in other parts of the body.

Not only do these pellagraderms frequently arise from exposure to the sun, but insults and slight injuries of various kinds may determine the outbreak.

The author recalls particularly an instance where a patient had suffered for many years with the vague and uncertain symptoms that characterize the earlier stages of pellagra, but who never developed the erythema until on one occasion he assisted in extinguishing a fire in the earlier hours of the night, and on the following day presented himself with well-defined pellagraderms on the hands, which was subsequently followed by the usual general symptoms. The patient stoutly affirmed that there was no evidence whatever of skin trouble on the previous day—an assertion that is entirely in keeping with the fact first established by Raymond that these lesions make their appearance with extraordinary rapidity.

The author has been repeatedly informed by pellagrins of education and intelligence that their troubles began with skin lesions which were evidently initiated by trifling injuries. Thus, one patient affirmed that he stuck a tack in the sole of his foot, which was followed by an infection, with an extension of the inflammatory process to the back of the diseased foot; somewhat later the lesion assumed the characteristics of a pellagraderm, followed by similar lesions on the opposite side and also on the hands. In another instance the patient was stung by a mosquito on the back of the hand, and this was at once followed by a typical pellagrous outbreak. In several instances patients have affirmed that they had slight blows on the hands, and that the erythema immediately followed. Such a connection was likewise shown in a case where the skin lesions developed on the soles of the feet in a patient who operated a motor car during the active stages of the malady,—this clearly resulting from the irritation caused by the constant use of the foot-gear. The author then sees no escape from the view that very frequently the external manifestations of the internal disorder—which we are unfortunately accustomed to regard as in themselves constituting this affection—suddenly make their appearance following slight injuries to those parts of the body in which the pellagraderms usually occur,—a predisposition existing in the tissues, as pointed out by Brugia, Neusser, Zilocchi, Raymond and others, as a consequence of altered innervation and lowered nutrition, and, the author also believes, in addition, from histologic changes in the skin itself in many cases. Just why the hands, feet and face are the points of predilection in the development of these lesions is not entirely clear, but it may be pointed out that, with the exception of the volar aspects of the hands and feet, where the skin is remarkably tough and resistant, pellagraderms manifest themselves by preference on those surfaces that are most subject to insult, whether it be mechanical, or from such physical agencies as light, cold and heat. Undoubtedly the most exposed parts of the body are the hands, and here we find that the pellagrous lesion is most common, and after them and in the order named, the face, neck, feet, the forearms, the arms, the shoulder

blades and the skin about the middle portions of the chest in front where the shirt is often left open while the peasant is laboring in the fields. We also see the lesion in rare cases develop on the scrotum and peritoneum.

Pearson has also observed that the skin lesions are especially apt to occur in those situations where there is pressure or irritation, as, for example, on the shoulder blades.

It should also be noted that the great Italian pallagrologist Gemma (1) called attention to the fact that pellagraderms occur by preference in those parts where bony structures lie immediately beneath the skin.

Finally, it should never be forgotten that exposure to the elements is generally incidental to and conjoined with the labors of the fields which begin in the spring, and that this is usually—at least for a time—followed by a lowering of the general vitality.

Following the typical erythemas of pellagra we frequently observe a condition of atrophy of the skin, which, becoming thin, loses its elasticity and presents a curious shiny, transparent, parchment-like aspect. If the statements of intelligent and reliabe platients can be accepted this change may be often found without a preceding erythema. When once established this lesion remains throughout life. This alteration is the consequence of the absorption of the collagenous tissues, and the degeneration of the elastin of the derma, there being left of the normal structures the sebaceous and sweat glands and larger arteries and veins with enough fibrous tissue around them to give a certain amount of support; scattered everywhere throughout the skin are open spaces evidently filled with fluids during life. It is in such areas that we find the curious hemorrhagic spots that are very common in the chronic forms of pellagra, attention to which was first called by Strambio; these lesions are evidently the result of the rupture of small blood vessels, and are usually, if not always, produced by injuries which, as a rule, are so slight in charalter that the patient is often not aware of their occurrence. They are most frequently observed on the backs of the hands and lower parts of the forearms, but may occur also in the feet and face. These lesions are, of course, in no way influenced by the erythema, and may occur at any season of the year.

Gemma (1) and later Majocchi (2) have likewise called attention to dilatation of the sebaceous glands resulting in the formation of small elevations on the surface of the skin, and having their site usually on the edges of the nose, on the cheeks, and more rarely on the backs of the hands and breast. The author has likewise observed in a number of cases of the more chronic form of pellagra a tendency to the formation of thick patches of comedoes symmetrically arranged on the forehead, on the alæ of the nose, on the cheeks, and on either side of the median line on the under lip; just how these alterations in the sebaceous glands are produced is not known, but they are not improbably the result of altered nutrition in the diseased areas.

The changes in the nails and hair are undoubtedly the result of lowered vitality of the tissues and of altered innervation.

Causation of symptoms of the alimentary tract:

Among the most prominent and characteristic of the symptoms of pellagra are those of the alimentary tract. The mechanism of the production of the lesions by which they are caused is very imperfectly understood. They sometimes constitute the only objective alterations encountered in this affection, or may precede the appearance of the pellagraderms, and are found in the mouth or pharynx, or manifest themselves in digestive derangements of the glands of the stomach and intestines. More frequently they come on quickly after the skin symptoms appear, and it would seem under such circumstances that they result either from an increased toxicity of the body fluids, or from derangements of the sympathetic nervous system. As is the case with the skin alterations, lesions of the alimentary tract are particularly prone to occur in those situations where the mucous surface is subject to mechanical irritation, and are most common in those areas where bony structures lie immediately below the surface.

Causation of mental symptoms:

It seems not improbable that the mental symptoms that not uncommonly occur during the course of pellagra have, at least in part, their basis in the organic lesions of the brain that we now know are so frequent and so profound in this terrible disease, but to just what extent they are responsible is by no means clear. Irrespective of such pathologic changes we know little of the causation of the pellagrous psychopathies. It has seemed to the author that they are particularly prone to follow in the wake of mental anguish, however produced, and often apear to be associated, especially in women, with the death of near relatives, and not uncommonly develop shortly following financial losses. There is nothing to indicate that they have any direct connection with the ingestion of mould poisons. Just why the psychopathies usually come on in association with the other classic clinical phenomena is by no means certain, though it would seem not unlikely that a general state of autointoxication develops following the appearance of any one of the characteristic symptoms—more particularly those of the skin—and as a consequence we now and then encounter marked disorders of the intellect, usually accompanied by pronounced disturbances in the other viscera. The author knows of no explanation of the fact that those forms of pellagra ushered in by mental symptoms are almost always fatal. On the other hand, where the other symptoms develop first, there seems no relationship between the severity of the attack and the frequence of psychic change.

There is little doubt that the pellagrous psychoses are primarily due to the imperfect cerebral development which undoubtedly so often occurs in the typically hereditary forms of the malady.

Causation of nervous symptoms:

Like the mental disturbances, the nervous symptoms that so often occur during the course of pellagra are unquestionably largely due to the organic lesions that are so pronounced and so wide spread in this terrible disease. In addition it may, of course, be the case that

the toxic state of the blood, that appears so frequently to develop during the acute attacks, may in a measure be responsible for many of the nervous disturbances from which pellagrims so often suffer.

Causation of other symptoms:

It appears in the highest degree probable that organic changes in the nervous system are responsible for the production of the other symptoms which are so common in pellagra, such as digestive derangements and muscular weakness, vertigo, cramps, etc. Like the phychic disturbances they appear particularly common in women who have been subjected to mental suffering, and likewise they have no necessary connection with the severity of the disease in other respects.

The mechanism of the production of pellagrous vaginitis is not understood, though it is also probably of nervous origin, and is most common in the severe forms of the disease.

Causation of periodicity in symptoms:

One of the most curious phases of this complex question is the extraordinary tendency of the external manifestations of pellagra to make their appearance in the spring. Just why this is we are, unfortunately, not in a position definitely to say, but nothing can be more certain than that such symptoms are the outward expression of a deep-seated malady that persists, and which is by no means to be regarded as cured in the interval between the attacks.

In explanation of the tendency referred to, various theories have been advanced. Thus it is thought by some that the coming on of the symptoms in the late winter and spring is a consequence of the poor food and unhygenic conditions surrounding the peasant during the winter; it is pointed out that he is largely confined to the house, which is often poorly ventilated, that he has but little variety in food, and that he suffers from a lack of the exercise from which he profits so abundantly in the summer months. It is thought that with the depletion of the system thus produced any latent trouble would be particularly apt to manifest itself at the time that the farmer begins the labors of the fields,—the bodily powers under such circumstances often being overtaxed; coincidently, the exposure to the sun which naturally occurs is undoubtedly of the greatest moment in connection with this phase of the subject, since it has been clearly shown that this is one of the most potent of the etiologic factors in bringing on pellagrous attacks.

In addition to the foregoing causes it is well-known that for some obscure reason there are many skin eruptions that have a marked tendency to develop in the spring—some of which conditions evidently being of a constitutional character. Likewise Mesnet has shown that dermography is much more easily elicited and is more pronounced in the spring. As a further example of this may be noted the curious, periodic manifestations of *rhus* poisoning, it being well known that in children the eruption produced by this plant often recurs about the same time of the year for a number of seasons after exposure first takes place.

A very strange example of this tendency to periodic recurrence is recorded by Stejneger in his well-known monograph on the poisonous reptiles of North America. On June 1, 1882, an employee of the United States National Museum was bitten by an *Elaps fulvius;* the victim came near dying, but felt quite well at the end of three days. Two months later pains set in in the bitten finger, and an ulcer developed in a few days. At the time that this record was made, which was twelve years after the incident just related, the man always began to suffer a few days before June 1st with pains in the injured finger, and this was quickly followed by the development of ulceration and dropping off of the finger nail. These attacks last about two weeks. This incident is said to be by no means unique.

It is likewise true that periodicity in development of clinical phenomena is sometimes associated with undoubted intoxications; it having been observed, for example, by Bang, Hoegh-Guldberg and Barkhausen that delirium tremens occurs in the spring in most instances, and Des Planches, in his classic treatise on lead poisoning, likewise shows that the symptoms come on in the great majority of cases in the spring and early summer months.

In this connection it should not be forgotten that Romaro (1, 2) thinks that pellagrous attacks are precipitated in the spring as a result of the fact that toxic ferments are formed in the embryo of maize seed at this season as a consequence of an attempt on the part of the grain to sprout.

Lastly the observations of Ceni (11) and his associates, and of Gosio (8) and Palladino (2) clearly indicate that the moulds only elaborate their toxines during moderately cool weather, and that in the warmest summer months no poisons are produced at all. These facts curiously correspond with the well-known tendency of the pellagrous symptoms to appear in the spring and fall, these periods being precisely those during which the mould toxines are most virulent.

Finally in this connection attention should be called to the admirable investigations of Huntington, which are recorded in his book on "Civilization and Climate," in which he clearly shows that both mental and physical activity are greatly influenced by season,—there being marked depression at the end of both winter and summer. When these facts are taken into consideration it would seem altogether likely that it would be at just such periods that the external symptoms of a disease like pellagra would most tend to make their appearance.

In concluding this phase of the subject the author would say that he feels certain that the most potent causes of the tendency of the objective symptoms of pellagra to come on in the spring are, first and foremost, the exposure to the sun, and, of only secondary importance, the debilitating effects of the sudden resumption of hard labor after the idleness and bad food of the long winter months. Other influences are probably of no great moment.

CHAPTER III

PATHOLOGICAL ANATOMY.

Not within the almost boundless realms of medicine have we perhaps a single disease that produces such widespread and profound alterations as those that occur in pellagra. For the most part microscopic, they were for a long time almost wholly unrecognized, but with improved technique we are now able to establish that not only are there lesions in the skin, mouth and alimentary tract, but that there are profound alterations in the spleen, kidneys, liver, gall bladder, lungs, heart, bones, and above all in the blood vessels and the central and peripheral nervous systems. The only other malady known to us which approaches pellagra in its power of producing widespread morbid change is syphilis, but even in this disease the lesions are very far from being so constant, and are never of such universal character. Indeed, the only parallel which we have to the remarkable changes observed in this malady are those that occur in old age, and such alterations, as first pointed out by Foà, quite curiously, very closely indeed resemble those found in this affection, though only rarely are they so pronounced; as will be, moreover, later seen even senility itself does not offer the extraordinary variety of changes that are found in pellagra, and we thus find that the two differ not only in the degree of severity, but actually in their nature. As will be likewise shown in these pages the pathologic changes, except in some instances where they are clearly due to the operation of inter-current morbific agencies, are beyond all question of a purely degenerative character, and have no sort of connection with the more acute, so-called inflammatory alterations that follow the invasion of the body by either animal or vegetable parasites. Notwithstanding the remarkable richness and very typical character of the morbid changes that occur in pellagra, and in spite of the fact that our knowledge of some of them dates back now almost half a century, and that the most important alterations have been thoroughly understood for the last twelve or fifteen years, it is most extraordinary that no one has as yet made a systematic attempt to correlate these lesions with the well-known clinical manifestations of the malady. That part of the medical world interested in this subject has never seemed able to get away from the conception that the very essence and being of this malady consists in the purely adventitious, periodic attacks which are beyond doubt merely the external expression of a deep-seated internal disorder, locally aggravated by entirely foreign and extrinsic morbific agencies. To consider the trinity of symptoms which make up the typical clinical picture of pellagra as being the malady itself were much the same thing as looking upon the tertiary manifestations of syphilis in the same way, or, to make the parallel even more exact, to regard the feeble step, the atrophic musculature, the altered power of digestion, and the wrinkled and atrophic skin of old age as themselves constituting this condition. It is then to the pathological histologist to whom we must look for light as to the causation of the symptomatology of this curious disease, and not to the theorists who have in the past contrived and who have up to the present time continued to keep this whole subject in a state of the wildest confusion.

The earliest writers on pellagra do not appear to have given any consideration to the pathologic alterations that occur in the bodies of those suffering from this

malady. Thus, while we find that Casal in Spain and Frapolli in Italy gave most excellent clinical descriptions of the more usual forms of this disease, no mention whatever is made of any attempt to determine the character and location of the anatomic changes which would naturally be assumed to be of a most marked character in an affection so deadly.

So far as the records show the illustrious Gaetano Strambio (1-4) was the first who made any serious attempt to investigate this most important aspect of the subject. Nowhere are the great powers of this remarkable observer more clearly shown than in connection with his pathological studies of pellagra, for, although he at that time totally lacked the means and methods which are now employed in the histologic studies of nervous tissues, his unerring judgment led him always to search in the nervous system for the cause of the phenomena which he was investigating. So much stress did he lay on this connection that his son, Giovanni Strambio, accused his father of being so much under the influence of his teacher, Borsieri, and his mind so dominated by the nervous symptoms occurring in the malady, that he, in his investigations, paid but little attention to the intestinal tract,—a reproach which he little merited.

The next students of the pathology of pellagra appear to have been the Italian Fanzago (1), and after him Nardi (2), Verga (1), Brièrre de Boismont, Carraro in Italy, and Alfaro in Spain.

The first work of a systematic character, however, which appeared on this subject was that of Labus, published in 1847, in which he gave the results of his findings in one hundred necropsies performed by himself, and almost an equal number by others.

Nothing could better illustrate the many difficulties presented by this disease to the pathological anatomist than the results recorded by Labus in this investigation. His report shows that of 100 cases selected 57 of them died of intercurrent affections. Of these 17 succumed to pneumonia, 10 to anæmia, 9 to tuberculosis, 5 to extravasation of blood, recent or old, 2 to pleurisy, 2 to hypertrophy of the heart, 2 to hepatic cirrhosis, 2 to enteritis, 2 to typhus, 1 to lardaceous degeneration, 1 to pericarditis, 1 to gangrene of the lungs, 1 to softening of the brain, 1 to capillary apoplexy, and 1 to tetanus. These results indicate clearly the greatly increased susceptibility to other diseases brought about by the pellagrous state, and naturally increase to an almost inconceivable degree the difficulties of the pathologist in determining just what changes are truly the result of pellagra and which are the consequence of intercurrent maladies.

Observations of a similar character were later made by Gintrac, and Lussana and Frua.

The results of the foregoing investigations were naturally exceedingly sterile and in every way disappointing, since it was not until after the beginning of the latter half of the nineteenth century that observers began to study histologically the changes that occur in this disease.

So widespread are the morbid changes in pellagra that it will be absolutely necessary for the sake of clearness to consider them in connection with the organs and tissues affected.

Although historically the alterations that are so abundantly found in the cord were fully described before those that occur in the brain, for the sake of convenience the latter will be considered first.

Brain. Gaetano Strambio (2-4), who first investigated the bodies of those dead of pellagra, surmised, as has already been said, with characteristic acumen that the of the most important pathological lesions in this disease would be found in the nervous system. Notwithstanding this deduction, the great pellagrologist of Legnano was unable to find anything of importance in these structures, though unquestionably his failure was the result of the inadequate means at his disposal for making such examinations.

Fanzago (1) likewise was unable to discover anything of importance as the result of the few autopsies which he made.

The first writer, however, who records any direct observations pointing toward the central nervous system was Lavacher de la Feutrie, who journeyed from France to Legnano to study pellagra under the elder Strambio. In his excellent monograph published in 1805, Lavacher says that in 16 post-mortems he found edema of the meninges 12 times, of the brain 8 times, and of the ventricles 3 times.

Alfaro, who appears to have been the first who made necropsies in Spain, records nothing respecting the changes of the central nervous system.

It was well along in the beginning of the nineteenth century before writers began systematically to make examinations of the central nervous system in pellagra.

In 1829 Joseph Frank published notes of three post-mortems by Villa made in 1789-90, and it is of extreme interest to note that this investigator observed that the brains in his cases were atrophied and the consistency greater than normal; it would appear that Villa's observation, the correctness of which modern investigation abundantly attests, was in reality the first recorded instance in which a condition of the brain was recognized that is now known to be very frequent, and of the greatest importance in connection with the pathological anatomy of the malady under discussion.

In the same volume Frank expressed the opinion that the malady is clearly of nervous origin. He says,

"The cadavers, so to speak, show nothing of a positive character, but to the eyes of the anatomist they present the appearance of having died of a nervous affection."

In 1830 Fantonetti noted the fact that the pia showed injection and was adherent as the consequence of inflammatory changes; he observed likewise softening of the brain and atrophy. In the same year Carraro observed that the meninges are thickened in this disease.

Liberali in 1831 wrote a somewhat extended treatise on the subject of pellagra, and particularly addressed himself to an investigation of the pathological changes which occur as a result of this disease. He found the meninges injected and other evidence of inflammatory change, along with punctiform hemorrhages in the brain, and increased consistency of this viscus.

In 1836 Nardi (2) called attention to congestion of the blood vessels of the meninges and brain, thickening or opacity of the dura mater, and in some instances an exudate on these coverings; this writer likewise noticed injection, thickening and opacity of the pia-arachnoid, which also occasionally showed an exudate, injection and softening of the cerebellum, and increased fluid in the ventricles and between the brain coverings.

In 1846 Girelli in 12 cases of pellagrous insanity observed a dropsical condition of the choroid plexus.

The year 1847 was notable for the publication of the works of Rizzi and of Labus, that of the latter being the first systematic treatise on the subject of the morbid anatomy of pellagra.

Rizzi described thickening and opacity of the dura mater and of the arachnoid, with injection of its blood vessels and punctiform hemorrhages in the brain and increased liquids in the cranial cavities.

The work of Labus was remarkable for the fact that he reported the results of examinations in almost two hundred post-mortems—no writer even to the present day having collated the findings in so large a number of cases.

In one instance only he speaks of the brain itself, and in another of capillary apoplexy,—these terms, of course, being too indefinite to indicate with any certainty the exact nature of the processes found. This observer also noted slight changes in the brain in pellagrims dying of intercurrent affections,—such changes being tortuosity of the blood vessels, an increase in the cerebrospinal fluid, and slight dilitation of the ventricles.

Gorno, in 1848, observed injection of the meninges, with traces of inflammation, punctiform hemorrhages in the brain, and increased consistency of this organ, with an atrophic condition of its cavities.

A. Verga (1), in 1848-1849 wrote two papers, in which he described post-mortem findings in 41 cases. In 21 of these the dura mater was adherent to the cranium and was opaque and thick; there was likewise thickening and opacity of the pia-arachnoid, with injection of the blood vessels; in 10 of his cases punctiform hemorrhages were found in the brain; the viscus likewise showed in some lessened and in others a increased consistence; the cerebellum was softened in 7 cases, and in 8 atrophy was found.

The next article of any importance on this subject is that of Gintrac, which appeared in his well-known treatise on the subject of pellagra in 1863. In speaking of the brain he says,

"The brain is rarely in a normal condition, its surface being frequently congested and likewise often soft. The meninges are in a state of hyperaemia; very frequently the spinal cord shows in the dorsal region a marked softening of the white substance."

This writer agrees with the conclusion of Strambio that pellagra is a chronic disease of the entire body.

A new era in the pathology of pellagra was initiated in 1862, when Benvenisti particularly directed attention to changes in the upper part of the cord which were found in every instance in 40 pellagrims, and two years later Bouchard (3) independently made a similar observation in a case of supposed pellagra examined in France. The lesions, which were in the lateral columns of the cord, were examined and their presence confirmed microscopically by the latter observer.

The next investigator whose results are of any importance was the celebrated Italian pellagrologist Lombroso (2), whose attention was evidently early directed toward the nervous system as being the probable seat of the important lesions of pellagra. In his well-known treatise on this subject, which appeared in 1869, he records that thickening and opacity of the meninges, edema and softening of the cerebrum and atrophy of the cortex occur; furthermore, there were recorded instances where obvious alterations were present in the cord, and a microscopic study of the tissues of the brain showed the presence of fatty and pigmentary changes in the ganglion cells of the cerebral cortex, and abundant corpora amylacea (p. 303). In the same year he wrote a paper in which he called attention to the fact that many of the symptoms of pellagra clearly show profound alterations in the ganglia of the central nervous system (1). This observer clearly had the nervous system in mind when, in 1871, he replied to those who objected to the maize theory on the ground that when the consumption of maize ceased the symptoms should subside, by insisting on the profound histologic changes probably produced by the poison, and pointing out that such alterations probably persist for a long time.

Notwithstanding that in the intervening period great progress had been made in the study of the changes that take place in the cord in pellagra, little more of importance was done until the year 1898, at which time Rossi (2) noted the fact that profound alterations likewise occur in the brain. This observer, working with Nissl's method, extended his observations to the ganglion cells of the cerebrum and there found alterations which corresponded closely with those which he had previously described in the cord. In the greater number of the cells of the cerebral cortex he found slight discoloration around their edges and a breaking up of the tigroid bodies, which appeared granular and disintegrated. Particularly in the second case studied the nuclei appeared shrunken and their reticulum more or less broken up, while in others these bodies were distorted and displaced toward the periphery of the cell. The writer noted great pigmentation in the cells, along with displacement of the protoplasm, and the formation of vacuoles.

In 1899 the investigations of Rossi were confirmed and extended by Babes and Sion. These writers showed that both in the medulla and cerebral cortex there are localized areas of sclerotic change resembling those found in the cord. There is likewise hyperaemia, proliferation of the endothelial cells, collections of small round cells, and swelling of the neuroglia cells around the blood vessels; these alterations are particularly marked about the basal portion of the zone of the pyramidal cells. In this area there are found, as a rule, small collections of mononuclear round cells collected about the dilated perivascular lymph spaces. There are likewise elongated cells containing yellow pigment, which are probably of endothelial origin.

The pyramidal cells suffer most, though the smaller nerve cells likewise show change. In the nerve cells there are found pale, swollen masses, or considerable collections of pigment about the nuclei, while the tigroid substance is decreased and pushed to the periphery; the nuclei are frequently dislocated and atrophic. These changes, while occurring scattered throughout the cerebral cortex, are most marked in the paracentral lobes. In two cases examined all of the cells in these areas were markedly altered, being devoid always of tigroid substance, and were finely granular, pale and swollen, with many vacuoles; the nuclei are often absent, or when present are dislocated, irregular in form, and atrophic, with pale, generally swollen nuclei. The cells have no processes except such as are swollen

and broken off; any pigment that the cells contain is usually at one side. The pericellular spaces are dilated and their outer walls are covered with small particles of yellow pigment.

Confirmation of the results described by Babes and Sion quickly followed, articles on the subject having appeared in 1900 by Rossi (4) and Grimaldi, and in 1901 by Kozowsky (1).

In 1903 Amabilino added to our knowledge of the structural changes that occur in pellagras insanity. This author observed that examination of the brain in such cases disclosed almost complete disappearance of the tangential fibres of the cerebral cortex, and in addition to this he observed the changes in the nerve cells already referred to.

In 1904 a noteworthy contribution was made to this subject by Camia, he having examined 7 cases with the result that alterations in the nerve cells of the brain were found in every instance.

Further advance in our knowledge of this subject was made in 1905 by Parhon and Papinian, who appear first to have examined the nerve cells of the brain and cord for changes in the neurofibrils. As might have been expected, the alterations in these structures were found to be less marked in the smaller cells of the brain,—the maximum change being in the cells of Betz. In the medium-sized cells the fibrils are less intensely impregnated than usual, appearing to be abnormally thin and even fragmented. In the small cells the fibrils are often found almost, or even entirely, normal. In the very large cells there is almost complete absence of the neurofibrils, while there is a striking mahogany coloration of their protoplasm; in some of these traces of fibrils are found around the periphery, and still more of them in the cellular prolongations. The nuclei, particularly in the cells of Betz, are atrophied or invisible, and the nucleoli are but little impregnated in the cells showing the greatest alteration.

The changes just described as occurring in the neurofibrils were confirmed by Valtorta (2) in 1908, this observer employing the method of Donaggio.

In 1911 Bravetta (1) described similar changes in the neurofibrils, and in addition observed that they were often twisted, thickened and frequently formed spirals.

Similar results were obtained in 1912 by Rezza, there being complete fibrilolysis in those cells which present glassy degeneration. Contrary to the observation of Parhon and Papinian, this writer was unable as a rule to trace the neurofibrils into the protoplasmic prolongations of the cell; this, however, may have been the consequence of a difference in technique. Rezza employed the method of Bielschowsky, while Parhon and Papinian only mention that they used a silver impregnation process.

In 1912 Millant reported some observations on the neurofibrils of the cells of pellagrims made by Urechia; while the results indicated lesions of these structures in all parts of the nervous system in this disease no alterations of a characteristic nature were found.

In 1913 Singer and Pollock noted agglutination in the neurofibrils, and likewise observed a tendency on their part to form spirals around the nucleus or pigment masses.

In typical pellagra, and also in cases of "pellagra sine pellagra," the author has observed extreme fibrilolysis, being present in some cases to such an extent that scarcely a cell could be found in which these structures were preserved.

Gregor, in his well-known monograph on pellagrous insanity, written in 1907, mentions the fact that examination was made of the brains of seven of his cases by the method of Nissl, and that in all marked pathologic changes were demonstrable. A difference in the localization of the process was only noted in so far that in one of the cases with marked dementia the anterior portion of the brain was particularly affected. The writer remarks that cases of chronic character, with termination in dementia, differentiated themselves anatomically from cases with more acute course, though the precise nature of the histologic changes in question are not stated.

In 1908 the Hungarian writers Lukacs and Fabinyi reported pathologic findings in 3 cases of supposed pellagra, though much doubt is thrown on the diagnosis by the fact that all three of the patients were confirmed alcoholics. The uncertainty in these cases is accentuated by the fact that no alterations were found

by the writers in the layer of large pyramidal cells, nor do they refer to changes in any part of the brain other than the gyrus centralis, in the deeper layers of which the cells are much altered. The changes observed are that the cells bcome swollen, homogeneously granular, lose their nuclei, and stain throughout in a uniform manner. A milder form of the degeneration is evidenced by the cell-body shrinking, and the tigroid substance being irregularly displaced and finely divided. The nuclei are cloudy, and they are stained too little or too much, and the nucleoli often show the presence of small dark bodies. There is marked evidence of neurophagony; these writers regarding the process as being likely initiated by the glia cells.

The subject of the alterations in the brain in pellagra is very fully discussed by Marinesco (7) in his classic treatise on the nerve cell which appeared in 1909. This author speaks with so much authority and the description which he gives of the changes is so clear that it may not be out of place at this point to quote rather extensively from his remarks on the subject of the alterations that occur in the nerve cells ofthe cerebral cortex. He says:

"As is shown by the studies of Babes, Sion, Righetti and those made by myself, there are encountered in pellagra lesions which have a special physiognomy. Not only do they present certain special peculiarities, which will be presently described, but these lesions are peculiar in the fact that they are so widely scattered throughout the nervous system. Indeed, they exist in every part of the cerebral cortex, from its anterior to its posterior portions. They are only found in cases of pellagra accompanied by mental change, so that I feel authorized in making the statement that there is a connection between the two. On the other hand they are lacking where there is only a pellagrous erythema without mental symptoms."

"All of the convolutions of the brain present much the same cellular change,—the lesions found in the ascending frontal and paracentral lobes being taken as the type. In a general way it may be said that the somatochromes are more altered than the caryochromes. Not a single cell of Betz escapes the pathologic change—the larger having lost their pyramidal form and having become rounded and globular, with fewer prolongations; the tigroid substance is altered in different areas, undergoing in some instances chromatolysis, resulting in a veritable dissolution of its elements, while in others the change is partial; in some cases the cell has more or less lost its chromatic substance, and appears pale and looks like frosted glass."

"When the solution of the chromatic substance is incomplete some of the tigroid bodies escape, and those that remain present varying appearances: there are wavy filaments, concentric, and having an orientation different from that of the normal; this depends beyond doubt upon their plasticity. There are likewise corpuscles and granulations of unequaled size. The dissolution of the tigroid substance is very irregular, which explains the formation of stained and unstained areas."

"Achromatosis occurs usually in the cells which are becoming atrophied. As I think I have shown, in every instance where the relation of the elementary granules to the chromatic substance is interfered with the former finally disappear, producing a state of achromatosis. The nucleus no longer appears normal, is often displaced and pushed to the cell wall, with which it appears in many instances to be united. When it is found in the center of the cell its form is frequently preserved, being often surrounded by an atmosphere of chromatic substance: if, however, it abandons its position, it changes its form, becoming elipsoidal, oval, or kidney-like."

"The cells in a state of partial or general achromatosis are invaded by the yellow granulations which are known as pigment, and which are a pathologic product. Conjoined with these alterations which occur in the giant cells there are also changes in the pyramidal neuroglia cells, the latter augmenting in volume and multiplying in numbers, though this reaction is not constant."

"The large pyramidal and medium-sized cells of the cerebrum present, at least to a certain degree, the lesions which occur in the cells of Betz. The cells in the bulbar nuclei are likewise diseased." (Vol. ii. pp. 392-395).

And again:

"Similar changes are found in the optic cells, the nuclei of the larger pre-

senting characteristic lesions consisting in a central dissolution of the tigroid substance, the displacement of the nucleus, and a swelling of the cell body."

"The cells of Purkinje are the only ones that show an exception to this rule, for they are always found entirely normal."

"Righetti, who has published a very interesting work on polyneuritis of the spinal roots in a case of pellagrous insanity, observed lesions which resemble those seen in our cases, and he has admitted, in view of the researches of Ballet and my own, that the lesions which he found in the cord are secondary to the polyneuritis. Indeed, at first glance the alterations of the nerve cells in pellagra present in the main a great resemblance to those which result from section of peripheral nerves and from polyneuritis. I, myself, in the beginning of my studies on the nerve cells in pellagra thought for a time that the lesions were secondary to degeneration in the nerves. If this opinion were correct, one should find in all the cases of pellagrous psychoses where the giant cells are altered a constant degeneration in the pyramidal tracts, but in three cases where no such alteration existed, changes in the large cells were nevertheless quite manifest. It is, therefore, impossible to explain the alterations constantly found in the cells in the gray substance in pellagra by the inconstant lesions found in the white substance and in the peripheral nerves. We are, therefore, obliged to admit that the lesions of the gray substance in the brain and spinal cord in this disease are of a primitive character. Indeed, the type and variety of aspect of the lesions in these cells vary so greatly that the changes are only compatible with the view that the lesions are primitive. In my previous work I have already insisted on the variability of the cellular lesions in this disease, and have noted that unlike what usually happens when nerve cells are directly attacked by a poison we have here lesions principally of the protoplasmic prolongations of these bodies; this explains the diminution, oftentimes very considerable, in the number of the prolongations which we find in these cells."

"When the nerve itself is the seat of primary change, two varieties of alteration occur: at first there is degeneration scattered throughout the cell body, following which there is degeneartion of the nerve fiber at the point where it emerges from the cell."

"Alterations of the peripheral nerves and of the white substance is not very frequent. My conclusions are that these degenerative changes are secondary to alterations in the nerve cells, the great multiplicity of which proves to my mind that the changes are primitive." (Vol. ii. pp. 397-399.)

In 1909, at the meeting of the First Pellagra Congress held in the United States, the writer (2) published the results of his investigations in 5 cases of pellagra. Changes in the nerve cells similar to those observed by the foregoing authors were described by him. It is particularly noteworthy, in view of Marinesco's statement that cellular alterations in the brain substance occur only in the insane, that the case studied by the writer in which the most pronounced lesions were found—the subject was a negro woman who died of pellagra after several weeks illness, but who preserved her mental equilibrium up to within a day or two before death—had at no time previously shown evidences of insanity. It is likewise true that the cells of Purkinje showed advanced alterations—these bodies indeed being in the majority of instances completely destroyed, and presenting only granular remains (see illustration). Cerebral edema was evidenced by the fact that the layers of the cerebellum, which are divided from each other by the layer of Purkinje's cells, were completely separated in many situations by what was evidently merely serum. It is, therefore, clear that Marinesco's statement that the cells of Purkinje are never diseased is erroneous.

In 1912 Zilocchi published a very interesting article on the pathologic alterations found in two cases of pellagra, special attention for the first time having been given to the changes that occur in the basal ganglia; it is to be regretted that in both instances the subjects were past middle life, being aged 50 and 56 respectively. In the first case the brain was flaccid, congested, and edematous, and in the second similar changes were present, with the addition of spots of pachymeningitis of recent date, a thinning of the corpus collosum, the optic ganglia, and caudate nucleus; the white substance of the parietal and temporal regions was softened and atrophic. Some portions of the arteries composing the circle of Willis were hard and atheromatous.

The specimens were hardened and stained in the usual manner. On microscopic examination there was found a great abundance of lypochromes scattered throughout the nervous system; the white substance showed marked degenerative changes in many places, particularly in the cord.

In the first case there was marked degeneration in the bulbar nuclei, with atrophy of these bodies and increase of neuroglia in limited areas,—this change particularly occurring in the space around the back part of the internal capsule, where the fibers of sensation pass into the corpus collosum. Gliosis occurs to such an extent that the fibers are separated from each other. A similar area is found in the corpus collosum. The lumina of the vessels in the bulb are filled with white corpuscles.

In the second case, in addition to the microscopic lesions of the corpus collosum and the atrophy of the ganglia throughout, there are present cellular lesions, resulting in degenerative changes of a marked kind and even disappearance of the cells. The cells of the adventitia of the blood vessels are abundant, and also the neuroglia cells around these vessels.

In the same year Rezza published the results of his study of three cases,—the patients—as has been usually the case in such investigations—were unfortunately insane; however, in many ways this article is one of the most important that has as yet appeared.

The tissues were prepared for examination by the most modern methods, free use having been made of the technique devised by Alzheimer for the investigation of nerve tissues.

Meninges.—On examination of the *pia-arachnoid* there were found many fibroblasts; some of these presented numerous fine granules, sometimes obscuring the nucleus, to which is imparted an intense green color when stained with toluidin blue; similar cells have been described in progressive paralysis and in tuberculous meningitis. More numerous are fibroblasts with elongated nuclei and pale protoplasm; pear-green granules are present in the protoplasm, which the writer regards as lipoids. Other cells—some larger and some smaller—are found which resemble "kernchenzellen"; they contain pigment which stains green with toluidin blue. Other elements were found, the true character of which the author does not feel that he can definitely determine. The blood vessels show decided proliferation in their wall, with here and there a mast cell; this is most pronounced in the adventitia.

Where the pia joins the brain minute microscopic hemorrhages were encountered. Within the hemorrhages there occur lymphocytes and a few polymorphonuclear and mononuclear leucocytes; there are likewise a few plasma cells. In the areas where the greatest reaction occurs a peculiar concentrically arranged deposit is found, which does not stain by the method of Nissl, and which is very refractive. In some areas drop-like masses lying near connective tissue cells are encountered, which show similar optical peculiarities, and in addition a finely stained nucleus in the middle; these masses are regarded by the writer as being identical with Robertson's concentric bodies. Similar structures have been found by Simchowicz in senile dementia. In the main, similar lesions are found in the meninges of the cord, though active inflammation is less marked, and hemorrhages are rarely seen. In the meninges about the posterior nerve roots certain elements are found which show a pale blue concentric nucleus and very clear nucleoli, and which stain an intense violet-red by Nissl's method; these bodies are clearly the granula of Reich, and are thought to consist of protagon. Such grandules have been recently found in great numbers by Kornikow in old people. Much fat is found in the pia of the cord by Hertzheimer's method.

In summing up the writer says that hyperplastic changes are found in the pia mater, with numerous retrogressive alterations, but with no evidence of actual acute inflammatory change. Most pronounced among these alterations is the presence of atypical fibroblasts filled with pigment, much fatty material, particularly in the coverings of the cord, the constant occurrence of Robertson's concentric bodies, and many cells with Reich's granules.

Vessels.—No marked changes are found in the larger blood vessels by Nissl's method. At the most there are observed in the outer coats pycnotic nuclei, around which are pigment masses of varying size, some remaining yellow and others being

stained green. Only rarely a lymphocyte may be seen lying on the inner wall of the blood vessel, with a clearly defined nucleus and faint marginal protoplasm.

With Hertzheimer's method fatty materials are found in the walls of both the smaller and larger blood vessels. In no case was there evidence of arteriosclerosis, such as would be indicated by thickening of the elastic layer, irregular contour of the capillary walls, etc. With Alzheimer's method No. 9 lipoid granulations may be found lying about those glia cells which are arranged along the walls of the blood vessels; sometimes there are great drops in which vacuoles are found.

Along the walls of the capillaries and small blood vessels Alzheimer's method No. 4 shows numerous small, round glia cells which appear to support the vessel walls. Only rarely was there evidence of the new formation of capillaries. Except that the walls of the blood vessels of the cord show a greater amount of fat, they present much the appearance shown by those in the brain.

In the blood vessels then we have, above all, evidences of degenerative change, shown by the fatty alterations in their walls, though there is no actual arteriosclerosis. Along the smallest vessels, particularly in the white substance, there are numerous small round glia cells which form muffs around them. Sometimes there is evidence of a relative increase of blood vessels.

Nerve cells.—While all of the nerve cells show characteristic alterations from the frontal to the occipital portions of the brain, these changes vary greatly in degree and character. The cells that are rich in chromatin, such as the pyramidal and Betz cells show most change; in Nissl preparations they lose their pyramidal form, becoming rounded or barrel shaped, and are often practically twice the normal size. The number of protoplasmic processes is not always decreased, but they often stain only for a short distance; as a rule the axis cylinder is not visible. The chromatic substance shows marked changes, this beginning in the middle of the cell, and, swelling, pulls the nucleus, and pigment where it exists, to one side. Where the chromatic substance has disappeared—and this may occur in the entire cell—its content shows a peculiar glass-like appearance, which is called by Brugia hyaline swelling or hydropic degeneration; where this change exists no structure can be discerned; in some cases such masses have a faint granular structure or may appear to contain vacuoles. These masses are looked upon as being quite characteristic, though Alzheimer has described more or less similar structures in several diseases of the central nervous system.

The nuclear membrane has an irregular angular contour, with indentations, with intensely basophilic masses clinging to it. The nucleus is pushed to the periphery of the cell and takes on the contour of the surface against which it lies; where it is dislocated into one of those portions of the cell from which processes arise, the nucleus may take on a triangular form.

The nucleolus is generally enlarged and contains two or more vacuoles; it generally occupies the most peripheral portion of the nucleus. In these cases the nucleolus may entirely disappear or may be found lying outside the nuclear membrane.

Fatty pigments are sparingly present in cells showing these changes, and are generally found dislocated toward the periphery; sometimes they occur in pocket-like protrusions of outer portions of the cell. Rezza reaffirms the statement, notwithstanding Marinesco's findings, that pigment is only sparingly present in these cells.

The neurofibrils were investigated by Bielschowsky's method, and it was found that in the pyramidal and Betz cells these structures are twisted and broken up,—it being possible to trace only a few of those that originate in the cell processes. In the central portions of these cells, where the peculiar hyaline substance already referred to is present, no structure can be determined by this method; here, however, vacuoles of varying size and number are frequently present (see illustration). In these preparations the slight amount of pigment in the cells is seen drawn to the periphery, forming a thin border, and there is often a network in the meshes of which there is a gold-like substance. In the other ganglion cells these changes are not so marked, but are unquestionably present.

It is very interesting to note that in one case, a 66-year-old woman, Rezza found Fischer's plaques. The writer observes that even in this case he was unable

to discover the peculiar thickened neurofibrils described by Alzheimer in senile dementia.

Glia.—This observer noted a very great increase in the glia cells and a slight increase in the glia fibers. In Nissl preparations there are many typical glia "stäbchenzellen" as well as much characteristic "gliarasen." These are more numerous in the outer layer of the cortex, in which the chronic type of cell change is most marked. There are also found in this area regressive alterations, though these are not of a marked character. There are likewise found many small deeply stained irregular nuclei that contain numerous chromatin granules. In the outer zones of the convolutions Weigert's method shows a slight thickening irregularly distributed; there is furthermore demonstrable a thick fibrillary network, though there are not found the characteristic bundles of fibrils observed in progressive paralysis and other diseases. When stained by Herzheimer's method the protoplasm of the glia cells shows moderate amounts of fat, a condition also seen in specimens stained by Alzheimer's method No. 9. In all of the cells there is a zone of stained granules, in addition to a deeply colored, deformed nucleus. By Alzheimer's method No. 4 all sorts of irregularities are found in the processes of the astrocytes in both the white and neighboring gray substance. In the protoplasm of the astrocytes there are many vacuoles of various sizes which may be entirely empty or contain masses of golden pigment. Between the processes of these cells one finds the small round glia cells which are everywhere numerous,—particularly along the smallest blood vessels. The nuclei of these elements as a rule show small vacuoles, or, in some cases, larger ones that cause the nuclear membrane to bulge. Amoeboid cells are also found, though they are not numerous; as to whether these cells take their origin from the astrocytes or from the small cells this writer is uncertain, though he is inclined to think that both of these cells normally may undergo such a transformation—the former as the result of regressive and the latter as the consequence of progressive change.

In 1912 Kozowsky (2) published the most extensive article which has as yet appeared on the pathologic changes in pellagra. This writer's work was carried on in the Kostjuschener hospital, which is located in the Russian province of Bessarabia. It is to be regretted that an investigation which goes so thoroughly into a study of the anatomic changes in pellagra should not also have included at least a few examinations of the bodies of subjects dying of pellagra who had not become insane. His work, however, is noteworthy in that he has eliminated all cases past middle life, and has been the first to enlarge on the idea that the changes observed in pellagra are very similar to those seen in old age, a fact which has been insisted on from the clinical standpoint by Sacchi, Foà (1), G. B. Verga (1), Lombroso (11) and Alpago-Novello (2). Kozowsky deserves great credit for this conception, which alone would be sufficient to make his work noteworthy; but when we add the labor necessary to investigate thoroughly histologically the tissues of 16 dead pellagrins, the writer's article becomes truly monumental. Unfortunately its usefulness is somewhat marred by frequent inaccuracy in references, and the misspelling of the names of the investigators to which reference is made.

His investigations of the *brain* have resulted as follows:

Meninges.—The *dura* is in the majority of cases normal; sometimes it is whitish and thick, the inner surface showing hemorrhages only exceptionally; the *Pacchionian bodies* are moderately developed, the blood vessels engorged with blood, and the *pia* almost always opaque and thickened along the blood vessels, but easily removable; exceptions to these findings are rare. Now and then bony plates are found. The blood vessels of the pia are filled with blood, but show no evidence of inflammation of a chronic kind.

Brain.—Sometimes there is an appearance of edema of the *brain*, which is often connected with the very common atrophy of the cerebral cortex. The larger blood vessels at the base of the brain are usually normal, though they occasionally show slight initial arterio-sclerosis. The very occasional appearance of fibrin and polymorphonuclear exudates are simply accidental, and indicate secondary infection. The brain is always greatly sclerosed in all of its parts, and only now and then, when edema is marked, do we fail to find this change present with naked eye. Exceptionally the pia is adherent to the brain. The superficial portion of the brain shows the appearance of passive congestion, there being often

numerous small openings in it (état criblé), and, in addition, punctiform and larger hemorrhages. The white substance, in comparison with the gray cortex, appears swollen, which is the consequence of increased blood in the former and atrophy of the latter. Similar changes are found in the basal ganglia, there being état criblé, sclerosis, hemorrhages, and now and then cysts containing serum.

The *cerebellum* is likewise sclerosed, and occasionally contains hemorrhages.

The lateral ventricles are rather often greatly dilated.

Lime salts are ffequently found deposited in the choroid plexus.

The floor of the fourth ventricle shows no particular change.

The ependyma are normal.

The medulla oblongata shows no pronounced alteration.

Nerve cells.—On microscopic examination the nerve cells of the brain are found almost always more or less altered, the change occurring in all parts of the cortex and in the ganglia and nuclei of the cerebral nerves.

The most constant and general alteration is the accumulation of pigment in the cell-body; this change is not only found in the central nervous system, but similar alterations occur in the cells of the sympathetic ganglia. The pigment is often present to such an extent that it takes up the entire cell-body, replacing the protoplasmic structures and the nucleus, and causing the cell to break down; from the foregoing it seems clear that the pigment is not simply deposited in the cells of the central and sympathetic nervous systems, but there is in reality a pigmentary degeneration. Particularly beautiful alterations of this kind were found in the nuclei of the facial and hypoglossal nerves.

As respects the other changes, they may be classified as follows:

(1) Uniform degeneration of the tigroid substance into fine granules. This change affects the entire cell and causes the disappearance of the nucleus.

(2) The tigroid substance disappears in the neighborhood of the nucleus and is only preserved around the edge of the swollen cell.

(3) The whole cell body becomes homogeneous and structureless, and the nucleus disappears.

(4) The cell degenerates into a number of masses which are stained blue by Nissl's method.

(5) Vacuolization of the cell body.

(6) The cell becomes smaller and the staining power of the tigroid masses is altered in such a fashion that they appear massed together; the nucleus is smaller and becomes elongated, and its content stains intensely; ultimately the cells become still more compact and lose all internal structure.

The nucleus often takes a peripheral position, and at the same time losing its contour, shrinks, and ultimately disappears. Finally it must be noticed that some of the swollen cells that have lost their power of taking stains become bladder-like in form and much larger than normal.

Kozowsky is strongly of the opinion that the degree of cell degeneration largely depends on the length of the period of mental change—the more protracted the case the more pronounced the alteration.

He is by no means disposed to accept the view that the changes observed in the nerve cells are all of primary character. As proof of this he mentions the fact that Righetti, Marinesco and he himself have observed cases with neuritis, and on post-mortem examination secondary changes in the nerve cells were found in the cord which were clearly the result of the peripheral lesion; under such circumstances the primary pathologic state is the one which, of course, deserves most consideration. The writer is fully in accord with Marinesco, in that he assumes as certain that there are in many instances alterations in the cells of a primary character.

An analysis of the changes in the cells referred to shows that change No. 1 corresponds closely to the granular degeneration of the chromophile elements described by Ewing. Very similar is the significance of change No. 2. Both alterations are primary, as is shown particularly in change No. 2 by the nucleus retaining its central position. Change No. 3 corresponds to what Schmaus has called "homogeneous swelling." The disappearance of the nucleus and sharply marked changes in the chromatin are the signs of a cell disease, the nature of which "much too little is known for us to give any definite opinion" (Schmaus). The [illegible]rations observed in change No. 4 occur in advanced cases; in acuter forms of

the disease the tigroid substance may be observed lying outside of the cell body and degenerating, with the formation of intensely chromophilic granules. Changes Nos. 3 and 4 are considered nearly related. As regards change No. 5 much caution in arriving at a definite conclusion is necessary, since some look upon it as being pathologic, and others as resulting simply from post-mortem change; some even regard it as normal. The writer is quite sure that it is not a post-mortem alteration in his experience, since in every case the tissues were fixed immediately after death; he is, however, not so sure as to whether or not it be an artifact, since the alteration is more common in tissues fixed in alcohol. Nissl regards this alteration as pathologic. Change No. 6 the writer mentions that Nissl first described as a chronic cell disease.

As respects the pigment which is so freely scattered throughout the nervous system, attention should be directed to the fact that it is usually of a yellowish color, though occasionally it appears brownish. It is deposited in greater or smaller masses, sometimes occupying the periphery of the cell and sometimes its whole body. In the latter case it replaces the nucleus. The pigment is likewise found in the neuroglia cells and in the walls of the blood vessels. It is insoluble in ether and alcohol, but is colored black or brownish by osmium. Although it is well-known that these pigments occur in normal cells, the quantity present in the nerve elements in pellagra is certainly pathological. Its increase is unquestionably the result of a physiologic degredation of the cell. The writer agrees with Babes in the view that this pigment is produced from the chromophilic substance, and appears to be in accord with Marinesco's theory that it is produced by a slow degenerative change,—fat resulting when the pathogenic agency is of such character as to produce acute alteration.

It is noteworthy that Nissl maintains that whenever there is a displacement of the nucleus a lesion of the cell undoubtedly exists—a view which is accepted by all writers. Further than this, however, nothing can be definitely said,—particularly as to the duration of the change, this writer (2) having subsequently shown that we have no way in the present state of knowledge of determining how long these alterations have existed.

Neuroglia.—Microscopic examination of the neuroglia shows that nuclei are numerous in both the white and gray substance; these were found on careful examination to be the nuclei of neuroglia cells, and the following varieties may be differentiated:

(a) Nucleus round and not particularly large, containing little chromatin and only staining here and there; the protoplasm is scarcely noticeable. The cells are found in the pericellular lymph spaces, and in some instances completely filling them, though there may also be present the remains of the destroyed nerve cells in addition; other cells in these situations are rare. It is also true that these cells occur in the neuroglia, forming small masses or chains.

(b) The nuclei are all medium-sized and pale, with marked surrounding protoplasm.

(c) Large, egg-formed, pale nuclei. The protoplasm is clearly differentiated, and presents a sharply defined contour.

(d) These are cells with two large pale nuclei in a large mass of protoplasm. They occur in the gray substance, the central ganglia, and to a less degree in the white substance. In the superficial layers of the brain there are a few small shrunken angular nuclei that stain intensely and have scarcely any protoplasm.

Spider cells are comparatively rare, having been found only in one instance in any considerable number.

Only in exceptional cases were *monster glia cells* observed.

In addition to the increase in the cells, glia fibers occur in thick networks,—being principally present in the outer layers of the brain substance and in the deeper portions, particularly along the blood vessels. The arrangement of these fibers shows no abnormality. They are found also in the central ganglia, and occur in the white substance of the brain and cord, the pyramidal tracts and posterior columns being particularly affected in the latter viscus.

From the foregoing it is evident that in pellagra there is a widespread process, causing in the central nervous system proliferation of the neuroglia structures, as is evidenced by an increase in the glia fibers, and, to even a greater extent, increase in the glia cells, which often present mitotic figures.

Cells *a* to *c* inclusive are found in the normal neuroglia, as was shown by Nissl. Somewhat different is the case with cell *d*, the presence of which indicates a progressive cellular development.

The glia cells in the subpial tissues are normal.

The spider cells cannot be regarded as indicating disease. Astrocytes are exceptional, and are to be distinguished from the ordinary spider cells by their large size and their microchemic reactions.

The writer now discusses the significance of the changes found in the glia, prefacing his remarks on this subject by giving the opinions of a number of writers as to what the different changes observed indicate.

The growth of the pia to the brain is regarded as being a reparatory process.

The small dark angular cells containing pigment may be looked upon as evidence of retrogressive change.

The writer expresses himself as being still undecided respecting the significance of what is called neuronophagia.

The question is next discussed as to whether from the changes found conclusions may be drawn as to the length of the process. In discussing this phase of the subject attention is naturally first directed toward the spider cells and astrocytes, which, though not present in great numbers, are still quite often found, particularly as the presence of the latter would indicate that the process is of a chronic character. This conclusion is strengthened by the presence of a considerable number of small-cell elements and the development of reparative neuroglia fibers. The presence of the spider cells indicates repeated exacerbations, with intermissions, which corresponds accurately with the clinical picture of pellagra. Particularly worthy of notice is the formation of glia fibers in the white substance; such new formations occur in masses of two different kinds, one being connected with the blood vessels and the other not; in the latter there are no "gitterzellen," so that here beyound doubt there is a long drawn out process of local degeneration followed by reparative changes and the development of glia tissue.

As regards the changes in the intracranial nerve fibers, the writer mentions that Binswanger many years ago called attention to the fact that many normal fibers do not stain properly and that more recently the best observers have maintained the truth of this view, and it, therefore, follows that any conclusions in this connection must be drawn with great care. It is even asserted by Cramer that normal fibers may give the appearance of those that are degenerated. With these observations in mind, the writer still maintains that he found many fibers which were swollen, varicose, irregular in form. and which stained poorly. There is, however, no regularity in this alteration; it is noteworthy that such changes are sometimes found in the subpial and supraradial layers, while in other instances they are absent.

The writer now takes up the subject of the *mesodermal portions* of the central nervous system—first, however, discussing certain peculiarities which are characteristic of the histology of these parts. As shown by Nissl, normally neither lymphocytes nor leucocytes are present in the walls of the vessels; it is likewise true that the adventitial coat not only acts as a covering to the vessel, but is likewise the histologic boundary between the mesodermal and epidermal portions of the nervous system. There are two lymph spaces, one between the muscularis and the adventitia, and the other between the adventitia and the glial perivascular limiting membrane. These spaces are separated from each other where the adventitia exists, but when the latter does not occur, or is only present to a slight degree, the two lymph paths unite with each other.

The writer next takes up a discussion of the plasma cells and agrees that they probably have their origin in lymphocytes. According to Nissl all those cells which are not "gitterzellen," fibroblasts, lymphocytes, leucocytes, endothelial and mast-cells, are plasma cells.

Alterations in the *blood vessel walls* have already been referred to; it was found that we have under such circumstances swelling of the intima, loss of staining power in the endothelial cells, and hyaline degeneration in the blood vessel walls; there is also swelling of the endothelial cells of the capillaries. In addition there is often found fragmentation of the muscularis, and in some instances this coat takes on hyaline changes similar to those found in the intima.

followed by loss of staining power in the contained nuclei. It is noteworthy that much pigment is present in the adventitial coat and in the endothelial cells. The elastic fibers of the larger blood vessels split up into several layers. It is likewise the case that scattered throughout the brain and cord small hemorrhages are not uncommonly found, with a resulting compression of the neighboring small blood vessels. In both the brain and white substance of the cord there are small cavities, the walls of which consist of a stroma containing no nervous tissue. Finally it is noteworthy that the smaller blood vessels often appear ruptured and show evidences of passive congestion.

Exudative changes are rarely observed. Only in cases of acute pellagra does one find here and there around the blood vessels a few lymphocytes and leucocytes. Plasma cells are practically never encountered.

Attention is now directed to the cyst-like cavities that occur in the brain, to which the writer has previously referred. Reference is made to the fact that Marie has described three different kinds of cavities which occur in the brain, and which he distinguishes as follows:

(1) Disintegration cavities (foyers lacunaires de désintégration).
(2) Sieve-like state (état criblé).
(3) Cerebral porosis (porose cérébrale).

Leaving out the first of these as not corresponding with the condition present, and the last, which is probably an artifact, the result of gas formation, the writer particularly directs attention to the second, the so-called état criblé. This condition he regards merely as the result of frequently repeated congestions in the blood vessels, he having been able frequently to find the remains of the blood vessel walls within them.

The *corpora amylacea* are looked upon as being altered glia cells.

The writer says he has often examined the peripheral nerves, and has seen in the fine fibers of the extremities undoubted degenerative changes—such alterations even being present in the nerve endings.

In 1912 Singer and Pollock published a review of their findings in fifteen cases of what was believed to be pellagrins. Unfortunately, like almost all of the cases heretofore subjected to careful examination, the patients were insane, and under such circumstances one cannot but feel that the diagnosis is too uncertain for us to place absolute confidence in the results.

These writers call attention to the occurrence in their acute cases of Meyer's "central neuritis"—a condition which had been evidently previously observed also by Kozowsky. These changes consist in very severe axonal alterations, often involving practically all of the cells of Betz, and many of the large pyramidal cells of the central convolutions. Changes of a similar kind were found in ganglion cells of the internal ganglia. In the cord these alterations were constant and extreme in the cells of Clarke's column, and to a less degree in the gray substance. Similar changes were observed in the posterior root ganglia, and in the semilunar ganglia and in Auerbach's plexus.

In the nerve cells these authors found the changes that have been described by other writers, but were not quite so successful in demonstrating systematic degenerations in the tracts of the cord, though evidence of such change was not entirely lacking. They noted some degeneration of the fibers of the anterior and posterior nerve roots, this being most marked in the cervical region.

It is rather singular, inasmuch as five of these cases were said to have suffered from senile dementia, that no Fischer's plagues were found, nor did they note the peculiar swelling of the neurofibrils to which Alzheimer has particularly directed attention in this disease.

The authors regard the condition described by them as characteristic of an intoxication, though of no particular poison. They found no evidence of local infaction.

Wussow has recently studied a pellagrous brain chemically by the method of Koch, but found nothing characteristic.

Spinal cord.—While some of the earliest pathologists regarded the spinal cord with suspicion, naturally, as the important lesions are microscopic, nothing of consequence was discovered during this period. Although it is true that Liberali (2), Verga (2), Labus, Nardi (2), Marchi, and Brunetti all met with and recorded trifling alterations, no real progress was made in this direction prior

to the publication of Benvenisti's paper in 1862. In this work the writer mentions four cases in which the cord was softer and whiter than normal, and in one harder.

The next works of importance were those of Tonnini, published in 1883-1884. These papers may be considered as the foundation of our knowledge of the true anatomic changes in pellagra, and as a consequence forming the groundwork of the modern conception of this malady.

Tonnini investigated fifty-one cases.

Microscopic examination showed anaemia of the meninges eight times, being present in six women and two men; arachnoidal hemorrhage was found in four women; opacities and thickening of the meninges occurred sixteen times in thirty-one cases, and calcareous infiltration of the arachnoid twenty-seven times in fifty-one cases—the latter change being almost exclusively on the posterior and posterio-lateral aspects of the cord; in one case alone the lesion was found in the anterior portion. The foregoing changes were confined almost wholly to the lower portion of the dorsal and the lumbar regions—rarely occurring in the cervical portion of the cord.

Asymmetry of the cord was usually present. Anaemia was frequently observed, being much more common in women than in men. Hyperaemia and diminution in consistency and softening occurred in twenty cases out of fifty-one. In thirteen instances miscroscopic examinations were made; the changes found will be discussed in connection with the miscrocopic anatomy of the cord in this disease.

Neusser (1) in 1887 published his well-known monograph on the subject of pellagra. In his discussion of the pathologic alterations he mentions opacities, thickening, and adherence of both the cerebral and spinal meninges; he likewise noted softening, sclerosis, and atrophy of the cord.

The next contribution of importance to this subject was made by Belmondo (1, 2) in 1889-1890. After noting the usual changes in the meninges and cord to which reference has already been made, this writer took up the microscopic study of the tissues and completely confirmed and greatly extended the work initiated by Tonnini. From this time onward it was recognized that the gross lesions occurring in the cord and its coverings are of secondary and of really little importance, the attention of succeeding investigators being directed practically altogether to the study of the microscopic changes found in these tissues.

The next great advance in our knowledge of the changes in the central nervous system in pellagra was due to Rossi (1), who published in 1898 the first of his papers showing that profound alterations occur in the nerve cells in this disease.

A description of the histologic changes in the cord and its meninges is now in order.

The first microscopic examinations of the tissues of the *cord* in endemic pellagra appear to have been those of Lombroso (2), the results of which were recorded in his book on this subject published in 1869. This author described extensive pigmentation in the ganglion cells, and abundant corpora amylacea in the tissue of the brain and cord. In one case where a whitish-yellow lesion was found in the middle and upper dorsal regions miscroscopic examination of the tissues was made by Golgi, with the result that there were found in the area of the alterations noted considerable loss of myelin, and the presence of a large number of round, quite granular, nucleated bodies of a diameter of 30 to 60 μ; many of these bodies were surrounded by fine filaments, with a granular protoplasm, which now and then divides into one, two or three prolongations. The neighboring connective tissue cells were more than normally rich in delicate protoplasm, as were their prolongations.

In 1880 Bassi made a microscopic examination of the cord from a pellagrin, and noted a very remarkable proliferation of the ependyma of the central canal, In addition there were found sclerosis and thickening of the walls of the blood vessels in the anterior gray matter, and in the same situation numerous corpora amylacea. In seven cases this writer described a degeneration of the gray substance beneath the ependyma covering the floor of the fourth ventricle, some millimetres above the blind foramen, and corresponding to the ala cinerea.

In 1883-184 followed the classic work of Tonnini, already mentioned, and which undoubtedly forms the groundwork of our more intimate knowledge of the

whole subject of pellagra. Notwithstanding the fact that our technical knowledge was not at that time sufficiently advanced to permit exact histologic examinations, many of the changes found by Tonnini are now known to be universal in pellagra, and explain in a way that would be otherwise impossible the clinical course of the malady.

Microscopically this observer found great pigmentation of the cells of the anterior and posterior horns in eight cases, complete disappearance of the nuclei in many of the cells in one instance, and in others the contour of the nuclei was found to be ill-defined; the protoplasm of many of the cells was granular and cloudy, as a consequence of granulo-pigmentary degeneration. Atrophy of the cells was encountered in three cases, once in the cervical and dorsal segments, and twice in the lumbar. In two cases degeneration of the lateral columns of the cord was found; in one of these the process was so far advanced that it was apparent to the naked eye, but the other was in its incipiency, and while not visible macroscopically was found on examination to be present from the cervical region down to the middle of the dorsal portion of the cord. In the former there was lessening in consistency and granulo-pigmentary degeneration of the cells of the gray matter, accompanied by incipient degeneration of the posterior columns, and the usual opacity of the arachnoids and calcareous infiltration. In one case there was marked degeneration of the posterior columns, being limited to the lumbar region.

In 1885 De Hieronimis claimed to have found small round celled infiltration in both the white and gray substance of the cord in a case of pellagra, and similar changes beneath the ependyma of the ventricles; he likewise described a dilitation of the perivascular and pericellular lymph spaces. This writer also called attention to proliferation of the cells lining the central canal of the cord, as well as those of the ependyma, and, in the neighborhood of such changes, inflammatory alteration was observed in the surrounding tissues.

Three years later Marchi reported the results of a bacteriological and histological examination in two cases of typhoid pellagra. Microscopically he found that the posterior columns stained less intensely than normal by the method of Weigert, the alterations becoming more marked from above downward. By this writer's well-known method (fixation in 1 per cent. osmic acid in water one part and Mueller's fluid two parts) he demonstrated extensive degeneration in the anterio-lateral columns; he likewise found pronounced pigmentary degeneration in the nerve cells, though this, on account of its frequency in other diseases and even in normal individuals, is not regarded as being of any importance.

In the same year Tuczek (1) published the first of his papers on this subject. This article was of a preliminary character, his final results having appeared some years later.

In 1889 Belmondo likewise published the first of his illuminating articles on this subject. After the examination of eight cases the author arrives at the following conclusions:

"According to my investigations there occur constantly in pellagra, therefore, in its severe forms, systematic lesions, which include the posterior and lateral columns of the cord, thus forming a combined sclerosis. These lesions are always accompanied by alterations in the pia and changes in the gray substance."

In the same year Belmondo (2) published the beginning of his second paper, which appeared in several installments, and which was not completed until the following year. He says:

"In all of the cases examined there was encountered in the spinal cord a degeneration of the fibers of the crossed pyramidal tracts; this, however, varies in degree from a mild alteration consisting in a lessening of the fibers in transverse section, scarcity of myelin, and rarification of the tissues on the one hand, to more severe alterations on the other, accompanied by marked sclerosis, particularly in the pyramidal tracts, where one cannot observe in the field of the microscope a single normal fiber. Such alternations have been found in our cases to be for the most part very extensive, including the greater portion of all of the course of the pyramidal tracts. It is, nevertheless, always noteworthy that the greatest intensity of the process presents itself in the dorsal portions of the cord, and for

the most part in the lower two-thirds of this region; in the more advanced cases the change extends in the same degree to the end of the fibers of the lumbar cord."

"Commencing at the upper portion of the dorsal region the alteration increases downward, and going upward there remains only slight change at the cervical enlargement. In a small number of cases, where the lesions are much less marked, alteration is limited for the most part to the middle third of the dorsal region.

"Together with these lesions of the lateral tracts there is demonstrable, however, in all of our cases a well-marked alteration of the posterior columns of the cord. It consists in degeneration of the column of Goll, limited for the most part on transverse section by the medial fibers of the same, and being separated from the gray commissure by a small number of fibers which ordinarily remain normal. There is likewise a similar alteration of Burdach's tract, where these fibers lie next to the posterior root zone, and is particularly marked in that part of the column through which the fibers of the posterior roots penetrate to the cord. Differing with Tuczek I have not found this lesion to be at all rare, it being indeed one of the most common alterations observed.

"The most typical cases show an alteration of the posterior columns in every way similar to those observed in the beginning of tabes—with the difference only that whilst in the latter disease the lumbar portion of the cord is that which is most markedly diseased, in pellagrins we do not find the slightest lesion of the posterior columns below the middle of the dorsal region, with the possible exception of a slight degeneration of the central portions of the tracts referred to; rarely, the sclerosis of the posterior columns is perceptible through the entire lumbar region. In the pellagrins, moreover, the posterior columns are diseased always in a decided fashion in the cervical and upper dorsal regions, and at the point where these two portions come together we find, as a rule, the alterations most advanced. These findings are truly constant in the white substance, but in some cases there are united to them other changes which are not to be considered as exceptional. Thus, in two cases the process has included a tract situated anterior to the pyramidal fibers in the mixed zone of the lateral tracts, this change being limited to the dorsal region. In another case, limited likewise to the dorsal region, alterations are found in the fundamental tracts of the anterior columns in the region from whence the fibers of the anterior roots escape. In two cases in which the lesions of the crossed pyramidal tracts are pronounced the pathological process extends to the cerebellar tract. Here, however, the cervical portion of the cord is not diseased and the process is less marked in the pyramidal tracts, in which one observes many fibers that are normal, and less increase in the connective tissue.

"Together with the degenerations of the white substance described, we find in the cord of pellagrins alterations of the ganglion cells. These bodies are, as a rule, atrophic, diminished in size, with few processes, and even in young individuals loaded with pigment. This is especially noteworthy in the regions which are the seat of the graver alterations of the white substance, that is to say, in the dorsal region.

"The notable augmentation in the pigment in the ganglion cells just referred to is in some cases most marked, and has, according to our views, a particular significance, because, in addition to indicating that the nerve centers of pellagrins suffer marked disturbances of nutrition, it appears, contrary to the views expressed in recent writings, that there exists in reality a pigmentary atrophy of the ganglion cells—an atrophy which in fact consists principally in augmentation of the pigment."

The writer goes on to say that while he has noted complete closure of the central canal of the cord and proliferation of its epithelial lining, he does not attach any particular importance to this alteration.

He also notes abundant corpora amylacea, but as there was at that time no certainty as to their origin or their significance, the author contents himself merely with recording their presence.

He likewise called attention to the new formation of glia tissue encountered in two cases such as occurs in syringomyelia.

Again the writer says:

"The results of our researches then are that in pellagra, at least in its graver forms, we have systematic lesions of the lateral and posterior tracts of the

cord constantly associated together as a combined sclerosis. These changes are accompanied always by an inflammation of a chronic kind of the inner meninges, and likewise by alterations in the gray substance already described.

"Wishing to indicate more precisely the relative gravity of the various lesions we have to say that in the majority of cases there is a maximum alteration of the crossed pyramidal tracts. Likewise in the very pronounced instances of the disease the degeneration of the posterior columns is at one stage much less pronounced and limited to certain parts of the affected viscus.

"In six cases in twenty—three men and three women—the lesion in the posterior columns was found more pronounced than in the lateral portions of the cord, but these lesions are not proportionately so advanced as those which have been already noted in the pyramidal tracts; alone in the six cases cited this degeneration predominates over the other, for the reason that in the pyramidal tracts the lesion was only in its incipiency. In other cases several times the preparations presented the aspect of an amyotrophic lateral sclerosis of pronounced character; never could one have imagined from an examination of these preparations that they were from a case of advanced tabes, though they presented some resemblance to the changes observed in the latter disease during its sarlier stages.

"As regards the alteration in the gray substance, it is to be noted that the atrophy of the ganglion cells of the anterior horns never reaches in pellagra the great changes characteristic of amyotrophic sclerosis, as we have been able to prove by comparing our sections with beautiful preparations showing this disease which were made in the laboratory of the Salpêtrière."

In 1893 Tuczek (2) published a very interesting monograph on pathologic changes in pellagra, in which he completely confirmed the work done by Tonnini and Belmondo.

In his monograph he gives in detail the clinical histories and post-mortem findings in nine cases of typical pellagra, and in all found very marked pathologic alterations. In every case there were observed degenerations in the posterior columns,—Goll's column being diseased in all of these cases and the posterior median root zone in three. In six instances the lateral columns were affected.

In two cases there was an evident inflammatory change in the gray substance, being very marked in one instance; in the latter case the author found atrophy of the ganglion cells in the gray substance. Attention is likewise directed to the loss here and there of substance in the gray matter of the cord, with the result that cysts of considerable size are occasionally encountered.

Of great interest are the asymmetries of the gray substance of the cord shown more or less in six of his eight cases; in some instances there are marked deformities of both the white and gray substance, with here and there complete detachment of islets of grey substance from the anterior horns.

In the same year Mircoli reported four cases of pellagra with examinations of the cord, in all of which alterations were observed.

In 1894 P. Marie, following Tuzek, attempted to establish the view that in pellagra we have a well-defined system disease of the cord; he thinks that always there is degeneration of the pyramidal tracts, the comma of Schulz and in a degree the "zone cornu commissurale" and the "zone posterieure interne,"—thus being sharply differentiated from tabes.

In 1898 two articles on the pathological histology of the central nervous system were written by Rossi (1, 2), who appears to have been the first to examine these structures in pellagrins by modern methods. While previous writers had noted changes of a pigmentary character in the nerve cells, the credit appears clearly to belong to this observer for having published the first accurate investigations made in connection with what is undoubtedly the most important and interesting of all the changes that have been hitherto noted in this disease. Rossi found in the nerve cells of the cord a condition of advanced chromatolysis, sometimes affecting only the periphery, but in others the entire substance of these elements. The cells were often deformed, which was associated with corresponding loss of the tigroid bodies and the accumulation of masses of yellow pigment. In some instances the cells were entirely homogeneous, presenting a glassy appearance, but in other cases traces of the chromatic substance remained as a fine powder. Where the changes are advanced the nuclei are pushed toward the periphery or have disappeared entirely. The dendrites were greatly altered or entirely absent. In some instances only remains of the cells could be discovered.

In 1899 a very interesting case of pellagra was investigated and reported by Righetti. The patient suffered from a pellagrous insanity and developed a polyneuritis, with the usual symptoms. On microscopic examination there was found in the second lumbar segment of the cord an area of hemorrhags in the gray substance and of parenchymatous diffuse alteration of the cord both in its fibers and cells. The alterations of the cells are those usually noted. In the roots of the spinal nerves, particularly in front, there is a loss of staining power, with swelling and atrophy. By the method of Marchi there were found changes in the antero-lateral columns of the cord, particularly in the crossed pyramidal tracts, and in the columns of Flechsig and Gowers, but without circumscribed alterations in any particular system. In the bulbar region the fibers are degenerated in the crossed pyramidal tracts and inferior cerebral peduncles,—the change being symmetrical. It is noteworthy that the posterior roots showed in some sections marked degenerative change.

In the following year a very instructive paper on the pathology of pellagra was writen by Babes and Sion (1), in which were described changes in the cord. These writers in several instances encountered marked degeneration of the nerve fibers, particularly in the posterior root after passing through the ganglion, clearly indicating a degenerative process. In addition in one instance there were found around the nerve roots marked areas of inflammation containing swollen endothelial cells and plasma cells, and a few lymphocytes and connective tissue cells. The degenerative changes in the nerve roots may be followed up in the cord,—the resultant pathological picture closely resembling that seen in tabes; it is true that in pellagra Lissauer's zone, as well as the anterior root zone, is less attacked in pellagra than in tabes. In the gray substance the writers find in similar instances a prolongation of the changes in the posterior root into the posterior horns, accompanied in some instances by marked thickening of the blood vessel walls, and in others with the formation of granulation tissue in these areas. The writers note that Clarke's column is always attacked, all of its cells being swollen and oftentimes without nuclei. Similar changes occur in the anterior horns, particularly in the medial and lateral sections of the dorsal region. Here one frequently finds peculiar neuroglia cells with branching processes, which lie around degenerate nerve cells, and, taking their place, later form curious, radially arranged masses. The writers insist on the frequency with which *anomalies* in the architecture of the cord occur. They often find islets composed of ganglion cells completely separated from the gray substance, and have seen Clarke's column fully developed within the anterior horns.

They strongly disagree with Tuczek and Marie as to the nature of the sclerosis in the cord,—the latter writers looking upon the lesions as being of endogenous origin. Babes and Sion on the other hand take the view that the changes in the white substance are largely, if not wholly, exogenous, and they maintain that they by no means agree with the latest development of myelin covered fibers in the fetus.

In 1903 Amabilino noted lesions in the crossed pyramidal tracts and the usual changes in the cells in a case of pellagra, and in the following year Camia reported the results of the examination of seven cases, having found marked lesions in only two instances.

In 1905 Sandwith (2) reported a case, in which the changes in the cervical region were most marked in the columns of Goll,—the columns of Burbach being less affected; the lesion appears to have been of root origin.

In the same year Parhon and Papinian first reported observations on the neurofibrils in the ganglion cells of the cord. The neurofibrils are only found around the periphery of the cells and their prolongations, these changes being most marked in the lumbar and sacral regions.

Gregor in 1907 wrote an important article on the mental changes in pellagra, and recorded the results of the histological examination in seven of his cases. The usual alterations were found in the nerve cells. It is noteworthy that he found the cells in the posterior horns in all cases, particularly those of Clarke, markedly degenerated. The writer found lesions in the column of Goll and the crossed pyramidal tracts, and is thus in agreement with the findings of Tonnini, Tuczek, Belmondo, and Babes, but as regards Burdach's column he is not so completely in accord with these writers. In cases where intense degeneration

occurs in the posterior columns and in the posterior roots more or less change is observed in the fibers of the posterior root zone and in Burdach's column.

In 1907 Sandwith (3) wrote another paper, in which he reported the changes observed in three cases of pellagra. The alterations were found in the posterior columns, and appeared to have been of root origin in two cases, while in the third similar lesions were present, though only to a very slight degree.

Bravetta (1) found lesions in the ganglion cells such as described by others, and particularly noted great changes in the neurofibrils, which are often altogether absent. He observed scleroses in Burdach's column.

In 1909 the author (2) made the first report on the pathology of this affection published in America. In four out of five cases scleroses were found in the cord, being confined to the posterior and lateral columns. The nerve cells were found in every case to present marked degenerative changes, there being swelling and deformities of all kinds in their shape, and in some instances complete destruction. The nuclei were often found pushed to the periphery, and the chromophilic substance no longer stained in a normal way. Quite often the cellular content presented a homogeneous or glassy appearance, with only small remnants of the nucleus or the tigroid bodies (see illustration). The cellular processes were often destroyed. In one instance a typical acute meningo-myelitis was encountered. Although the post-mortem was made only a few hours after death, the cord was found very soft and on microscopic examination presented most marked alteration. The myelin sheathes showed pronounced degenerative changes, and the nerve cells of the gray substance exhibited to a high degree the alterations already described. Corpora amylacea were especially abundant throughout both the gray and white substances. It is noteworthy that in no case did he find the evidences of an acute process in the neuroglia, which, as shown by Nuel, consists first in much swelling, followed by shrinking, with great increase in the neuroglia network and the development of glia cells.

In 1911 Anderson and Spiller reorted two cases of pellagra, in which they found the cellular alterations described by all writers in the brain and cord. By the method of Marchi they were able to discover a profuse degeneration in the posterior and anterior columns in the first case, and in the peripheral portions of the posterior columns, the crossed pyramidal tracts, and the antero-lateral columns in the second.

In 1912 Kozowsky's (2) well-known article appeared on the pathology of pellagra. He mentions that the nerve cells of the spinal cord present alterations similar to those described in the brain, though in the former instance there is marked topographical distribution of these changes, they occurring principally in the anterior horn and Clarke's column; this peculiarity the writer regards as characteristic. The alterations are most common in the middle and lower portions of the cord.

As regards the degeneration of the white substance of the cord, this writer says that the lateral pyramidal tracts are those most commonly affected. In the posterior columns degeneration of the *zone cornu commissurale* and of the *zone posterieure interne* have been noted. Degeneration *en virgule* is not constant. The fact which principally contradicts the schematic theory of Marie is that there is degeneration in the posterior and anterior roots of Lissauer's zone, and when to this is added the softening areas which have been often seen by this writer in the white substance, he feels justified in maintaining that this theory does not correspond with the truth. The writer mentions that in some old pellagrins, who might have suffered from several other different diseases, he has seen pictures corresponding to those described by Tuczek and Marie, but even here there was not that sharply defined picture which the theory would require. The writer is not of the opinion that this change in the cord is of endogenous origin.

This writer also found that the blood vessels in the outer portion of the spinal cord are frequently obliterated and surrounded by connective tissue, with no nerve fibers. He has likewise frequently found small hemorrhages and the appearance of passive congestion. In general throughout the spinal cord fibrous tissue is found in increased amounts along the blood vessels and also the outer coverings of the cord are thickened.

In 1912 Rezza, in the article already referred to, described the changes found by him in the cord, which consist in a slight chronic thickening of the meninges, with evidences of an active process often less marked than in the brain coverings.

He finds in these tissues numerous cells containing the granules of Reich, which latter the author regards as protagon. It is interesting to note that these are frequent in the nervous system in senility. The pia contains more fat than the corresponding membrane in the brain. In the walls of the meningeal blood vessels there is much fatty material and many pycnotic nuclei, around which are pigment masses. The writer stresses the fact that there is no arterio-sclerosis. There was but little evidence of the new formation of blood vessels. Along the walls of the capillaries of the cord there are numerous small, round glia cells, which form collars about them.

The nerve cells of the cord show changes resembling those noted in the brain, though they are even of a more pronounced character,—all of the cells being affected. Weigert's method shows an increase in the peripheral glia fibrils and thickening of the bundles. Along the borders of the gray substance there are numerous glia cells, with twisted blount prolongations, in the protoplasm of which there are granules, and the nuclei in the majority of cases are completely degenerated.

The writer was unable to discover systematic lesions in any of the tracts of the spinal cord, and inclines to the view that previous observers have been mistaken as to the presence of such lesions. However untenable this view may be, it appears clear that lesions of this character are not invariable. He admits that he found small areas of degeneration scattered here and there.

Rezza concludes his article by saying that he observed in the pia both proliferative and retrogressive alterations; the blood vessels show no sign of arterio-sclerosis, but the fat in their walls indicates degenerative change. The ganglion cells show marked and characteristic alteration, while the glia shows progressive and regressive change; the white substance of the cord exhibits no systematic degenerative lesions, and real inflammatory foci are lacking.

More recently Singer and Pollock have contributed an interesting article on the histo-pathology of the nervous system in pellagra. These writers, however, add nothing of importance to previous knowledge further than the suggestion that the axonal changes are pronounced in pellagrins dying during an acute attack; where they recover and a period of time elapses before death occurs practically no such changes are present. These observers lay considerably more stress on an increase in the astrocytes than have other investigators. They observed evidence of degeneration in both the anterior and posterior nerve roots.

The fact that the cord changes described appear from their reports to have been present principally in the posterior columns, and their statement that in most cases the alteration in Goll's tract was most marked in the cervical region, leads to the suspicion that their cases may not have been endemic pellagra such as is present in the Southern States and in the pellagrous areas of the old world; slight variations in other particulars from the results obtained by European writers and those observed by the author,—such for example as lack of changes in the walls of the blood vessels—lend color to this suggestion. There can be no doubt that in sanatoria for the mentally weak the world over cases may be found, such as were called by Roussel "the pellagra of the insane," which do not resemble endemic pellagra in every particular, but which are generally so diagnosticated; from the knowledge at our command it may be also assumed that the two affections, at least to a certain extent, differ in their causation, and that their pathological anatomy is not identical. The fact that the eating of maize products is not so common in Illinois, where these observations were recorded, that all of the patients had previously suffered from mental disorders, that it appears that no attempt was made to ascertain if other members of their families had suffered from pellagra, and that no effort to determine as to whether the skin changes had followed a typical course in their development and evolution, altogether suggest the possibility that these authors were not dealing, at least in all cases, with epidemic pellagra; but, of course, the author merely suggests this as a possibility, and by no means intends to assert it to be a fact.

Spinal ganglia.—The earlier writers paid but little attention to the spinal ganglia, though Lombroso refers to pigmentation of the ganglion cells in one case in his monograph published in 1869 (p. 303). The first article on the subject was written by Bareggi (2) in 1883. He says:

"In these six cases the alteration of the spinal ganglia was not only constantly found, but the alterations were more marked in those ganglia that cor-

respond to the skin area commonly most affected, whether it be on the backs of the hands or the upper portion of the breast."

The alteration consisted in an extraordinary deposition of brown pigment in a greater or less number of the ganglion cells, being usually so arranged around the nucleus as to hide it, accompanied by a manifest atrophy of these structures, and to a greater or less extent of the fibers that pass from them. The proportion of the diseased cells varied in different cases, but in one instance was so pronounced as to affect all of these structures.

The next articles on this subject were those of Rossi (3, 4) in 1899 and 1900, in both of which he called attention to changes in the spinal ganglia in pellagra. Working with tissues stained by Nissl's method, he found a diffused disintegration of the chromatic substance, followed by a progressive decline in the power of taking stains of the granules that result from the breaking up of this substance,—the cell consequently assuming a diffuse bluish tint. The chromatin gradually breaks up and is reduced to a fine powder, which finally disappears in the cytoplasm. In many of the cells the nuclei lose their walls, are pushed to one side of the cell, and often entirely disappear. An increase in the neuroglia cells was likewise noted.

In the same year Babes and Sion (1) observed that the nerve cells of the spinal ganglia appear little altered, though they noted that between these elements there is often found a rich nerve fiber network, which they regard as being of new formation. Not uncommonly the spinal ganglia appear to contain an increased amount of fibrous tissue.

Some years later Amabilino likewise described alterations of the spinal ganglia, he having found that many of the cells shrink and their chromatin breaks up into fine granules and finally disappear. Accompanying this there are distortions and misplacements, shrinking and hypercoloration of the nucleus. In the cells less diseased there is a residuum of chromatin around the nucleus. In some cases the chromatin presents a diffused coloration, and in others the cytoplasm entirely loses the power of taking analine dyes. The cells show very conspicuous masses of yellow pigment. There is often proliferation of the connective interstitial tissue between the cells.

Sympathetic ganglia.—It has long been known that alterations occur in the sympathetic ganglia of pellagrins, attention having been first prominently directed to the matter by Foà in his work on the great sympathetic nervous system that appeared in 1873-1874, though Lombroso (4) refers to pigmentation of the ganglion cells some five years earlier, and in another paper says that many of the symptoms in this malady must come from disturbances in the ganglia (1). Foà observed that the ganglion cells are highly pigmented and that there is a pronounced hyperplasia of the interstitial connective tissue, associated with fatty change in the fusiform bodies. In typhoid pellagra this keen observer noted that there are infiltrations of small round cells abundantly present in the ganglia, and that the nerve cells show increased pigmentation, drops of fatty substance, and a protoplasm that is homgeneous and refractive.

Cavazzana, in 1894, showed that changes are constantly present in the nerve cells of the sympathetic ganglia in all intoxications, including pellagra. This has been confirmed by Angiolella, and by Noera.

Following the work of Foà this subject seems to have attracted little attention for a number of years, as we see no mention made of it until 1896, when the well-known book of DeGiovanni on the pathology of the sympathetic nervous system appeared. This author mentions that in ten autopsies he found notable external alterations in the sympathetic ganglia,—there being a pronounced thickening of the epineurium in three cases and a diminution in volume in five; he observed in nine instances sclerosis of the interstitial tissues and periarteritis, and in three subjects great pigmentation of the cells; in an equal number fatty changes in the fibers of the cells and in four atrophy of the cell body, with or without displacement of the nucleus, were observed (p. 112).

The most extensive work that has so far appeared on this subject is that of Brugia, who has, in an excellent monograph, reported his findings in fifty cases where the sympathetic system had been studied in persons dead of pellagra; on account of the fact that in twenty instances there were complications which might have vitiated his results, the author only drew final conclusions from thirty of his cases, there being fifteen men and fifteen women.

As the result of his labors he comes to the following conclusions:

(1) In all of the pellagrous insane whose cadavers were examined the sympathetic nervous system is affected, and the changes extent to all of their component parts.

(2) These changes in the ganglia of the neck and of the belly vary, depending upon whether the patient was suffering from the common form of insanity, or from the so-called typhoid pellagra.

(3) The prevailing form of alteration is an increase in the connective tissue to the point of sclerosis, a thickening of the walls of the blood vessels, a diminution in the number of nerve cells, along with atrophy, simple or pigmentary. Altogether exceptional is a form of hypertrophic degeneration.

(4) In an acute exacerbation of the pellagrous process the specific elements show a totally different appearance; rarely do we recognize atrophy, and we observe cloudy swelling of the cytoplasm, central chromatolysis of more or less extent, peripheral chromatolysis, complete lack of pigment, numerous lesions of the nucleus and nucleolus, and diffuse infiltration of leucocytes into the connective tissue (which commonly also invade the ganglion cells), proliferation of the endothelial cells of the blood vessels, circumscribed hamorrhages, and points and areas of softening.

(5) In every case, but especially in the chronic forms, there is a greater change in the abdominal ganglia (hypersclerosis of the connective tissues, and great atrophy of the nerve elements) than of those of the neck, and of both as compared with alterations in the gray and white substance of the cord. This predilection of the maize poison for the sympathetic nervous system is analogous to that which van Gehuchten has been able to demonstrate respecting the cerebrospinal ganglia in rabies.

(6) Nothing indicates as to whether the lesions of the nerves are primary or secondary; it is, however, probable that the active proliferation of the endothelium of the capsule, at least in some cases, goes hand in hand with the destruction of the cytoplastic elements.

(7) The acetonuria and the atonic diarrhoea so frequent in the pellagrous insane must be connected with the changes in the sympathetic nervous system of the abdomen, while the lesions of the cervical ganglia account in a large measure for the erythema, the constant dryness of the skin, the slight perspiration, and the alterations in the innervation of the pupil.

Changes in every way similar to those described by Brugia in the sympathetic ganglia have been observed by the author in his post-mortems.

It is of extreme interest to observe that in no instance has the author encountered more pronounced lesions of this kind than in a case of "pellagra sine pellagra." (The illustration at the back of this volume, showing the changes in the sympathetic ganglia in pellagra, is a reproduction from a microscopic section from this case).

More recently Obregia and Pitulescu have studied the neurofibrils in cases of pellagra, and have found most profound alterations. In addition they describe some very curious bodies in the sympathetic ganglia in both pellagrins and in senile individuals. They call them "reticular fibrillary glomerules," and assert that they are found at the ends of what appear to be afferent fibres, and lie in close contact with nerve cells, producing a sort of excavation in these bodies where they come in contact with them; as the fibres approach they usually make a bend, and then expand to constitute the glomerule,—the fibres radiating in every direction and anastomosing freely. Some of the larger glomerules are not in contact with the nerve cells.

The nerves.—For technical reasons it is obvious that no observations of any value could have been made on the state of the peripheral nerves by the older pellagrologists. It is, however, the case that some of the earlier writers were of the opinion that these structures are, at least occasionally, the seat of change in pellagra, since we find that Villa noted that the cranial and the first pair of spinal nerves in one of his post-mortems appeared to be hard and atrophic. On the other hand Fantonetti observed that these structures appeared edematous and swollen, reddened and soft, and Gorno spoke of injection of the neurolemma; Labus likewise mentions that he found the nerves augmented in volume.

The first accurate observations made on the peripheral nerves in pellagrins were those of Dejerine. His material was obtained from the dorsal surface of

the hands in two cases, the tissues having been removed within an hour after death. On examination it was found that very few of the cutaneous nerves were normal, their sheathes being in a large measure empty, and exhibiting the usual changes found in parenchymatous neuritis. In one of the cases the trouble was evidently quite old.

Many years later Righetti reported a case of multiple neuritis affecting the lower extremities in a pellagrin exhibiting mental symptoms. The roots of the spinal nerves—particularly those coming from the anterior portions of the cord—showed swelling, atrophy, and loss of staining power; both sets of nerves exhibited changes that characterize parenchymatous neuritis.

Somewhat later Rossi (4) observed alterations in the peripheral nerves,—a condition which had been previously deduced on clinical grounds by Mariani. He found proliferation of the nuclei of the primitive sheathes, alterations in the white substance of Schwann, and changes in the axis cylinders. The end organs quite generally showed atrophy, and the nerve fibers were disintegrated and only discoverable by the presence of Henle's sheath. The nerves supplying the tendons and muscles were normal. The author concludes from his observations that the pellagra-poison is probably exogenous, and that it affects both the central and peripheral nervous systems.

In the same year Babes and Sion (1) noted marked changes in the larger nerves and in the spinal nerve roots,—particularly those arising from the posterior portion of the cord; in one case the nerves in the latter situation were surrounded by granulation tissue consisting of swollen endothelial and connective tissue cells, plasma cells, and a few small mononuclear leucocytes. In some cases the posterior nerves, particularly after passing through the ganglia, fail to take the myelin stain of Pal,—the sheathes containing blue-black masses, and pale-brown granulation substance, and the axis cylinders being swollen and vacuolated. In two instances the nerve content failed to stain altogether, the white substance and axis cylinder having entirely disappeared. In the area of the blood vessels small round-cell infiltrations were found; some of the blood vessels were dilated. The writers conclude that there was evidence of a perineuritis, and a parenchymatous and chronic interstitial neuritis.

In 1912 Kozowsky (2) likewise noted evidences of degenerations in the nerves and nerve endings in the peripheral nervous system.

Heart.—Authors are generally agreed that in the earlier stages the heart presents no noteworthy alteration.

Strambio observed pericarditis, while Fanzago and Verga (1) both noted cases where the walls were relaxed and the viscus small. Frank (1) found the organ exsanguinated, discolored, and its muscular structure altered, and Nardi (2) also observed a like condition in two cases. Labus found in fifteen cases out of one hundred that the viscus was hypertrophied or atrophied. Baruffii noted that the heart was small in one case. Lussana and Frua stated that the organ is generally small, somewhat discolored, soft, and surrounded with fat.

Lombroso (11) calls attention to the fact that probably in many cases of supposed hypertrophy the appearances leading to such a conclusion are deceptive, the condition being in reality one in which the heart appears enlarged owing to its being flaccid. In twenty-six hearts weighed by this writer only two surpassed —and that only to a slight degree—the normal, five were slightly less in size than usual, while the remainder showed a great decrease in weight. Lombroso found very generally brown atrophy, it having been discovered twenty-eight times in thirty-five examinations, and the organ showing likewise an appearance as though the heart fibers had been pulled apart in many places. In three instances this observer found a fatty condition of the organ, and in one a marked deposition of pigment in the fibers.

Kozowsky (2) likewise called attention to the increase of brown pigment in the heart muscle, and also noted an increase of the fibrous structures of the organ,—this change being particularly marked along the blood vessels. The coronary arteries have thick walls, with their inner coats hyaline, and the veins enlarged and filled with blood. The cells of the heart ganglia are greatly altered, the protoplasm granular, the nuclei in the periphery, and the Nissl bodies granular or degenerated; the capsular endothelium is increased, as well as the interstitial tissue. In many cases the cells have degenerated into fine granular

masses, and in almost all of them there are enormous collections of golden pigment.

The writer in six post-mortems found the heart in every instance small.

Blood vessels.—Little attention was paid by the older writers to the blood vessel changes in pellagra. Lombroso (11) says that in one instance he noted a marked decrease in the lumen of the aorta. while in another case the opposite state of affairs existed; rarely atheroma was found, and even then only to a slight degree; in one case this change was limited to the splenic artery.

Kozowsky (2) says that there is no typical sclerotic change, and that the blood vessels present the same appearance observed in other diseases that have no relationship to arterio-sclerosis. This writes notes that in protracted cases of pellagra the heart and blood vessels are small, but he is inclined to consider this rather as the consequence of long-continued inanition than pellagra itself. As to whether the increase in the connective tissue of the heart is the result of changes in the blood vessels he is not clear, though he thinks where demonstrable alteration exists in the walls of the vessels such a relationship is probable. As particularly pointed out by this writer, changes in the smaller blood vessels are so diffused that they deserve special consideration. In the small arteries the intima is swollen frequently to such a degree that the vessel is almost closed; similar alterations occur in the other coats, the tissues losing their nuclei, becoming homogeneous, and appearing to amalgamate with each other. Such changes may occur in any or all of the organs, but are invariable in the spleen, in the kidneys, the liver, and the nervous system. Newly formed fibrous tissue is occasionally found around the blood vessels, though unaccompanied by a cellular exudate. Such changes in the spleen lead to degeneration of its follicles, in the liver and kidneys to cirrhotic changes, and in the central nervous system to destruction of the nerve tissues.

Daniel has recently described a pellagrous phlebitis in the legs.

Lungs.——That great pellagrologist Strambio (2, 4) called attention in his earliest writings to the common occurrence of lung complications in pellagra, he having particularly found a tuberculous condition very often; this writer was so impressed with the frequency of the latter alteration that he even went so far as to assume an especial form of tuberculosis due to pellagra.

Among the earlier writers not only Strambio, but Fanzago (1) noted the frequent coëxistence of the two diseases, the latter writer having found pulmonary tuberculosis in two cases out of six of his earliest post-mortems. Labus also observed that the two diseases commonly occurred together, having found nine instances of tuberculosis in his first one hundred post-mortems. Morelli in thirty-five autopsies was unable to find the slightest evidence of tuberculosis. In connection with this subject it is of interest to note that Lussana and Frua state that they were able to find clinical evidences of consumption in but three cases out of 600 female pellagrins examined by them.

It may be remarked at this point that this view has been combatted by others, first by the great statistical writer Calderini (1) and later by Garbiglietti, Gozzano, and others who have insisted that not only are tuberculous affections uncommon in pellagra, but that there is an actual antagonism between the two maladies.

In this connection the author would remark that he has never seen pellagra complicated with tuberculosis, and it would appear to him that, certainly in America at least, the former disease does not predispose to the latter. This is all the more extraordinary when one considers the extreme degree of lowered vitality that is characteristic of pellagra, and it would appear *a priori* that this malady would almost inevitably lead to tuberculosis, particularly in protracted cases.

Lombroso (11) called attention to the frequency in pellagra of pleurisy, pulmonary edema and hyperaemia, emphysema, and caseous pneumonia, which conditions were observed in nearly all of the necropsies made in Lombardy, while on the other hand in post-mortems made by this writer tuberculosis was found only four times, and three of these cases had practically recovered from this condition, as the nodules were surrounded by calcareous infiltrations. On the other hand this writer mentioned that in fifteen pellagrins examined in Trentino active tuberculous conditions were found nine times, and in one instance latent; in six

of these post-mortems atrophy and sclerosis of the lung were observed. Lombroso found in three instances pulmonary gangrene.

Kazowsky (2) found edema of the posterior lobes of the lung quite often, and on microscopic examination noted that there was a slight increase in the interlobular and peribronchial connective tissue, and congestion in the capillaries. In some cases there were slight microscopic areas of pneumonia, but otherwise the lungs were normal. The blood vessels of the lungs showed thickening, and in some instances hyaline degeneration of the smaller arteries. The areas of hepatization exhibited on microscopic examination the usual exudate of cells and fibrin; the writer regards this pneumonic state as being the consequence of the extreme state of inanition to which the patients were reduced before death, and thinks that the changes are directly due to the activities of bacteria which under ordinary conditions are present but harmless. In early cases this writer has occasionally seen typical pneumonia, and now and then pulmonary infarcts.

In six post-mortems the author found the lungs normal in every instance.

Liver.—The earlier observers paid but little attention to the liver; thus we find Strambio (2, 4) only occasionally alluded to the organ. In one instance he found it covered with tubercles, while at other times he spoke of it as being pale both internally and externally. He rather often notes the fact that the gall-bladder is distended and filled with thick yellow bile.

Fanzago (1) found the organ large, hard, and of a livid aspect in one case, while in another the consistency was increased, though the organ was normal in size; in still another instance the viscus was enlarged, adherent to the diaphragm, and the gall-bladder distended with bile.

It is much to the credit of Morelli that he insisted on the importance of the lesions of the liver, which he thought occurred more frequently than alterations of any of the other organs. Out of thirty-seven autopsies he found changes in this viscus thirty-one times. He says:

"As a rule the organ appears larger than normal; rarely its consistence is augmented, but more commonly is diminished, and becomes friable and soft on pressure. Its color is changed, being almost always yellowish, and presenting an anaemic appearance that extends through its entire substance. One sees the yellow acini very plainly, while on the contrary the red acini (veins?) and the blood vessels are decreased in size and somewhat obscured. In four autopsies the organ was found likewise discolored, but small and hard, and the whitish-yellow acini were so much enlarged as to resemble those of the salivary glands; they appear surrounded by a whitish membrane, which is very hard and fibrous. In another instance the organ was enlarged, but on section there was found scarcely any blood, contrary to the condition usually seen in hyperaemic states of the viscus; the gall-bladder often contains a whitish-yellow secretion." (p. 147).

Chiarugi found the liver yellow in twenty-nine examinations, and Verga (1) noted cirrhosis in two instances.

Lombroso (11) says lesions of the viscus are frequent, he having found the organ diminished in size eighteen times in thirty-nine necropsies, and in eight the gland presented the so-called brown atrophy. In twenty-seven cases the viscus was yellow and friable.

Carraroli (2) has found degeneration of the parenchyma, with fatty changes and atrophy; the beam-work may be somewhat infiltrated, and its characteristic structure deformed or lost.

Kozowsky (2) found in the liver cells quantities of brown pigment, with fatty infiltration and degeneration. In some cases albuminoid degeneration, and increase in interlobular connective tissue occurred. This writer asserts that he occasionally observed newly formed bile ducts. There was also dilitation of the central veins of the lobules, with decrease in size and hyaline change of the walls of the small arteries. The liver cells are sometimes atrophied by the pressure of the surrounding fibrous tissue or by the dilated veins. Mitotic figures were occasionally observed in the liver cells. The writer says that the change in this organ in pellagra consists in a combination of atrophic alterations of the parenchyma, with increase of interstitial connective tissue and alterations in the blood vessels. The pigment, which is so abundantly present in the liver, shows no iron, which, as shown by Kretz and others, is the case where death results from anaemia and inanition. Whether the sclerotic changes are the consequence of

passive congestion is a much mooted question, and one which cannot be answered in the present state of knowledge; we are not, therefore, in a position to say whether or not these two conditions which occur in the livers of pellagrins are associated or not.

In six necropsies by the author (4) the liver was found in every instance small and its consistence somewhat increased; in all, the viscera presented in a more or less characteristic fashion the appearances observed in brown atrophy. Microscopic examination showed increase of pigment, dilitation of the central veins of the lobules, venous congestion, and here and there a very slight increase in the interlobular connective tissue.

Some years ago the author observed in a young woman the development of pellagra immediately following an operation for a supposed appendicitis, and on recovery, the patient still suffering greatly from pains in the abdomen, it was determined to examine the gall-bladder, which was done some months later. The viscus was found to be filled with a thick, dark, cloudy bile, and its mucous surface appeared abnormally red and somewhat roughened and microscopically the organ presented pronounced alterations.

In two other cases specimens of the wall of the gall bladder were obtained during operations, and as the tissues were immediately fixed there could be no doubt that the changes encountered are present during life.

In all three instances the mucous coat of the viscus presented the red and granular appearance generally recognized by surgeons as indicating a pathologic state.

On microscopic examination it is seen that the mucous coat is thrown into numberless folds, the apices of which, as a rule. show the epithelial coating absent, and the outer layers of the submucosa are bare and form the inner wall of the viscus. Between these areas we see numberless desquamated epithelial cells which are rounded or irregular in form, granular and swollen, with loss of nuclei, and a granular acidophilic protoplasm. In places where the covering has not entirely disappeared a single layer of epithelial cells oftentimes represents the mucous coat, instead of the several strata that are encountered under normal conditions. In the underlying tissues there are evidences of acute inflammatory change in some cases, while in others the process is evidently chronic. In the former there are dilitation of the blood vessels and frequently enormous swelling of the walls, with the accumulation here and there of small collections of leucocytes, though alteration of this kind has only been once seen. In other instances the process is evidently chronic, and under such circumstances little or no swelling is present, nor are the blood vessels dilated, but there are found collections of lymphoid and plasma cells scattered throughout the tissues.

It is of great interest to observe that the celebrated De Giovanni has shown that the liver in pellagrins is almost uniformly ill-developed, and that it remains of small size throughout life.

Spleen.—According to Strambio (2, 4) and Fanzago (1), the spleen is sometimes soft, while in others it is tough and indurated. Fanzago noted a case in which the organ only weighed three ounces, the pancreas being likewise hard and atrophied. In another instance the organ was three times its normal size.

Carraro found in one instance the viscus very large.

Both Labus and Verga noted decrease in size of the spleen, the latter author maintaining that this change is particularly common in typhoid pellagra.

Lombroso (11) states that he found this organ atrophic forty-one times and increased in size in twelve instances.

Babes and Sion (1), however, state that the spleen is usually atrophic except in those cases where it is enlarged as the result of a complicating malaria.

Kozowsky (2) found uniformly thickening of the trebeculae in this organ and alterations in the walls of the blood vessels. In no other part of the body did the arteries show such exquisite changes as in the spleen. The intima is hyaline to a marked degree, obliterating in some instances its lumen entirely; occasionally all of the coats are hyaline (See illustration). With the increase of the interstitial tissue the cell-elements of the viscus diminish. The veins are enlarged and filled with blood. In some instances there is increase in the cellular elements, both of the pulp and follicles; the cells take on an epithelioid character, and in

these there are often found red blood cells; such cells frequently contain two spindle-shaped nuclei.

Gaucher and Sergent speak of similar alterations.

In six post-mortems the author found the spleen smaller than normal in every instance (4).

Kidneys.——The earlier writers generally considered the kidneys normal, though Morelli remarks that now and then they are atrophic and anaemic.

Verga (1) noted that these viscera in one case were of a yellowish color, while Gianelli and Festler both observed instances in which the kidneys presented the evidences of chronic Bright's. Vassale particularly called attention to the fact that the kidneys were frequently in a state of chronic parenchymatous nephritis.

Lombroso (11) found these organs fatty in twenty-one cases, in thirty-three atrophic and cirrhotic, showing cysts in five instances, and uric acid calculi in another; only rarely were they entirely normal. This author is of the opinion that uremic conditions are very common in pellagra.

Belmondo (2) noticed the frequency of chronic nephritis, as did also Poussie and Dide.

More recently Vassale, Roncoroni (3), Alpago-Novello (4), Zanon (1), Mannini, and Zanon and Vidoni have asserted that alterations in the kidneys, accompanied by hypertrophy of the heart and thickening of the walls of the blood vessels, are exceedingly common in pellagrous states.

Kozowsky (2) found marked dilitation of the capillaries, destruction of the tubules, thickening of the interstitial tissues, particularly near the periphery, and occasionally cellular exudates; Bowman's capsule was markedly thickened, and the glomerule now and then was composed of hyaline blood vessels. The epithelial cells of the tubules showed cloudy swelling and fatty degeneration, with the formation of hyaline tube casts, followed by complete destruction of the epithelium and collapse of the tubes. Masses of yellow and dark-brown pigment were found in the epithelial cells; this pigment did not give the iron reaction. The arteries of these viscera had thick walls, with hyaline inner coats. The walls of the veins were also thickened, and their lumina filled with blood. Such changes are those that are found in the kidney in passive congestion. While these alterations suggest arterio-sclerosis, this writer is hardly of the opinion that this is the case.

In sections from three kidneys examined by the author no appreciable alteration was found. It is furthermore worthy of note that only occasionally has he observed even traces of albumin in the urine of pellagrins, and only very rarely hyaline tube casts; it may be here stated that the absence of changes in the heart and blood vessels likewise indicate that arterio-sclerosis and Bright's are rare in American pellagrins.

It is interesting to note that Babes and Sion (1) found renal changes very rare.

Adrenals.—These structures appear to have been entirely overlooked by the early writers, and even Lombroso makes no reference to them in his book on pellagra.

No particular attention appears to have been directed toward these organs before the paper of Finotti and Tedeschi in 1902, in which they reported the results of the examination of the adrenals in nine cases, in all of which microscopic lesions were found; these consisted in thickening of the capsule four times; necrotic changes in the cortical substance three times; cellular infiltration five times; increased pigmentation four times; the most marked change discovered was that the medullary substance had entirely disappeared in eight of the cases, and showed cellular infiltration in the remaining one.

Kozowsky (2) found nothing but capillary haemorrhages in the adrenals.

Rubinato has described a case of pellagra, with symptoms of Addison's disease, in which the adrenals were found to be made up almost entirely of fibrous tissue.

O. Rossi also says that the nerve cells in these organs were rarely found normal in a case of typhoid pellagra.

The author has also found in the adrenals marked alterations, consisting in capillary haemorrhages, cellular infiltration, and destruction, with extreme fatty change, of the cells composing the medullary substance. Similar alterations of a

most pronounced character were found also in a case of "pellagra sine pellagra." (See illustration).

It is of extreme interest to note that Rondoni and Mantagnani have shown that in animals fed on maize there gradually develops in the adrenals a condition of pronounced degenerative alteration in the cortical cells, associated with an increase in the connective tissue frame-work of the organ, and finally followed by a decrease in the lipoids, which are normally present to a considerable extent in the parenchymatous tissues. It is of interest to note that Lucksch was unable to produce any naked changes in the adrenals even by prolonged hunger, so that it would appear that the changes above referred to are the result of some other disease producing agency than inanition.

Pancreas.—Writers have heretofore failed to discover anything of particular importance in the pancreas. Fanzago (1) noticed atrophy and induration in one instance. Lombroso found no changes in this organ, nor did Kozowsky. Barbieri has reported a case of haemorrhagic pancreatitis in a pellagrin.

Rubinato has recently observed an increase in the fibrous tissue of the interlobular and intercanicular structures of the pancreas.

O. Rossi found the cells of the acini often like those of the secreting portions of the gland.

Parotids.—Pearson has recently noted that the pellagrins of Egypt generally present a swelling of the parotid; unfortunately no studies have been made to determine the nature of this change.

Gastrointestinal tract.—One of the most frequent alterations in pellagra is the well-known changes that are so frequent in the mouth, and not uncommonly in the pharynx. These lesions may come on as the first striking objective evidence of a beginning pellagrous onset, and, indeed, in some cases they constitute the only visible lesion; in other instances they may follow the eruption and diarrhoea, or may be absent altogether.

The most frequent change is that observed in the tongue, which becomes reddened and inflamed, with swelling of the tissues and increase in the size of the papillae; in some instances the alteration proceeds no farther, but gradually subsides and the tongue returns to a practically normal condition. In other cases the inflammatory change rapidly increases in severity, resulting in actual ulceration, particularly under and around the edges of the organ. Where these inflammatory conditions of the tongue follow each other year after year there is frequently established a condition of hypertrophy of the superficial lingual tissues, and result finally in a great accentuation of the normal depressions that occur on its surface. Where the pellagrous state exists still longer, a gradual shrinkage of the tongue follows, causing the organ to appeal ultimately much smaller than normal. In all cases where the irritation of the viscus has existed for a long period of time its normal papillae are destroyed, and the covering layer of epithelial cells becomes gradually thinned, giving as a consequence a smooth and glossy appearance to the surface of the organ, which becomes at the same time much redder than normal owing to the transparence of the thinned outer covering. These alterations of the tongue are of great importance, since they often permit of a diagnosis being made in the intervals between the pellagrous attacks.

Changes similar to those that occur in the tongue are likewise observed on the gums and lips and buccal mucous membrane; where the process is severe there may be a very general stomatitis, which makes the proper feeding of the patient a serious problem.

As has been before remarked, changes of a similar kind also occur in the pharynx, though it is only very rarely the case that there is pronounced ulceration in this region.

Majocchi (2) has observed in some cases haemorrhages in the mucous membranes.

The very earliest investigators noted changes in the intestinal tract of those dead of pellagra, but these alterations were of such an inconstant and variable character that Strambio rightly looked upon them as being of no particular importance.

Fanzago (1) found the stomach contracted and thickened in one case, and in other instances the walls were soft and dilated.

Nardi (2) and Verga (1) observed the mucosa of the stomach injected, and Brièrre de Boismont in five cases found this, and a similar condition in the intestines, which were also soft and friable. Carraro likewise noted inflammatory conditions of the tract. Labus found the stomach normal in nearly 200 cases. Many observers have noticed redness, injection, softening, and friability of the intestines, along with thinning of the walls and induration; ulceration has also been observed, and likewise occasionally perforation. These ulcerations are present in the jejunum and ilium, with or without hypertrophy of Peyer's patches, the glands of Brunner, or the mesenteric lymph nodes.

Labus has particularly noted thinning of the intestine, which lesion he regards as constant in this malady. The change was never continuous throughout the entire course of the ilium, and always terminates a short distance above the caecum. The mucosa of the intestine, when showing this alteration, is almost always pale, with absence of the valvulae conniventes. This thinning is observable quite noticeably when the intestinal wall is held between the observer and the light. It differs from the thinning which occurs in diarrhoeas in that it is limited. This change has also been observed in two cases by Verga, and quite frequently by Mottini, though Morelli says he has only seen it rarely. The Piedmont Pellagra Commission of 1847, however, regarded this alteration as being inconstant, and did not accept the opinion of Labus that it was the characteristic lesion of the malady. Labus attributes this alteration to an atrophy of the muscular coat. Since the discovery of the characteristic lesions in the nervous system the change described by Labus has naturally become of little importance, and is no longer remarked by writers on this subject.

Lombroso (11) found anaema of the gastric and intestinal mucosa two times in seventy post-mortems, with hypertrophy four times and decrease in the thickness of the tunic twice.

Babes and Sion (1) found amyloid changes in the walls of the intestines in several cases.

Kozowsky (2) described a series of changes that are referably to chronic inflammation, with subsequent atrophy of the mucosa. Often where the other tissues of the intestine show no alteration this writer found marked changes in the nerve apparatus of its walls; the ganglia exhibited evidences of degeneration and show an increase of brown pigment. Several other observers have described a diphtheritic inflammation in the intestinal walls, and now and then polyp-like thickenings of the mucosa occur. In some cases Kozowsky found hyaline degeneration of the blood vessels, with complete obliteration.

Lymph nodes.—Babes and Sion (1) observed that the mesenteric lymph nodes, particularly in children, are often swollen and show the presence of tuberculous change.

Kazowsky (2) finds nothing in these nodes that is characteristic, though he says their blood vessels show hyaline changes, and around them the connective tissue is rather rich.

Adipose tissue and muscular system.—In the great majority of instances the bodies of pellagrins show a great decrease in the subcutaneous fat, though, as was pointed out by Strambio (2, 3), this is not always the case. Likewise the muscular tissues show atrophy, it having been noted by Lombroso (11) in twenty-one cases out of forty-four,—the other twenty being normal or robust.

In two instances the same observer noted fatty degeneration of the muscles, the change occurring in the pectoral muscles in one case, and in the other instance was limited to the inferior extremities.

Kozowsky (2) mentions that in protracted cases the muscles are atrophic, but says they show no other abnormality.

The skeleton.—The fact that the bones in pellagra are often greatly rarefied and very friable did not escape the keen eye of Strambio (1), he having noted it in one of his earliest cases. It was also early observed that fractures in pellagrins heal only with difficulty.

Lombroso (11) noted this alteration eighteen times in forty-two examinations, and observes that it frequently occurs in persons who are apparently in good physical condition.

Many other writers, among whom are Bouchard, Villargoit, Orsolato, and Suberbielle, have described this alteration.

Skin.—The gross skin lesions in pellagra are so numerous and complex and are so intimately associated with the clinical aspects of the subject that it has been thought wise, in order to avoid repetition, to describe fully these changes in the chapter on symptomatology, to which the reader is referred for a discussion of the peculiar characteristics that they present,—the histology only being considered in this connection.

The microscopic changes that are found in the skin in pellagra naturally depend largely on the character of the lesion under investigation, and, particularly in the more common forms, on the stage of the process. Although the skin lesions were studied microscopically by Calderini (2), the earliest systematic investigator in this connection appears to have been Griffini, whose well-known paper appeared in 1870. Unfortunately, however, this investigator does not make it perfectly clear as to how far the lesions had advanced when the sections used by him for examination were procured, though it is clear that in the three cases studied the process was not in any instance very old. The writer began by measuring the thickness of the skin and its various layers and comparing them with similar measurements from normal individuals. In two of his cases the several layers were thickened, this change being particularly marked in the outer epithelial coats. In one instance the writer thought that the connective tissues of the derma had undergone a change as the result of which they became homogeneous and glassy, but outside of this nothing of any particular note was discovered, except that in two cases there was marked increase in the size of the smaller blood vessels of the papillae, around which there were also collections of cells.

Raymond made a microscopic examination of specimens from the skin during the third stage. He found the epiderm thinner than normal, although there was an increase in the corneous layer and disappearance of the papillae. The epiderm is represented by two layers of equal thickness, the outer being the corneous layer which shows hyperkeratinization, while the lower half is made up of the granular and Malpighian layers,—the two being separated by a tissue of loose texture, in which there are cavities. The mucous layer is atrophied and the normal attachments which connect the cells are greatly altered. The cylindrical cells do not present any particular alteration further than an increase in their pigment.

The papillae of the derma are completely destroyed, and the blood vessels are greatly enlarged, contrasting sharply with the diminution in the surrounding connective tissue. The hair follicles, sebaceous glands and nerves are normal.

The most accurate description, particularly of the beginning stages of the lesion, is that of Babes and Sion (1), who begin the discussion by expressing the conviction that the characteristic alterations are tropho-neurotic in nature, and they state that they have often seen them accompanied by haemorrhage and even purpura in young persons. On microscopic examination they find in the derma a small amount of serous exudate, with a few leucocytes and a peculiar homogeneous, metachromatic substance, consisting probably of coagulated albumin, which is scattered throughout the tissues; in addition the sweat glands contain a greater number of cells and numerous metachromatic granulations. The nerves show nothing particularly out of the usual, except they seem infiltrated with a homogeneous substance that stains slightly, and which is relatively poor in myelin substance.

In the period of desquamation, and particularly after the process becomes chronic, these writers described pigmentation, scaling, and thickening of the skin. They say:

"Under such circumstances one recognizes a very peculiar epithelial development, characterized by the production of well differentiated layers of a thick homogeneous or porous material. The innermost epithelial layers contain much yellow pigment, while the papillae are in a condition of cellular infiltration and there are present numerous plasma cells; the sweat glands are increased in number and the dilated sebaceous glands often contain numerous colonies of a small diplo-bacterium, and in the neighborhood of these there is a granulation tissue which is either diffused or occurs in small masses; this granular tissue consists mainly of increased endothelial and plasma cells. The marked thickening of the skin is occasioned by the deposition of a peculiar tissue, which is partially formed of hyaline, of wavy thick fragmented fibers, which are connected with

rounded masses probably largely made up of an exudate, and to a still greater degree by degenerate elastin. In these tissues there are found numerous pale thick rods, which are sometimes doubled, that look like bacilli, but which are colored with analine stains only slightly. There is present here and there a peculiar condition of irritation, with exudation into the skin, which at least in the beginning may be compared with those peculiar erythemas produced in susceptible persons by eating certain foods, while at a later time there is a chronic sclerotic desquamative process which interferes with the function of the skin and which will be described by us in a future communication.''

Veress has likewise studied the skin in pellagra, his cases, however, having been evidently of a more chronic character than those described by Babes and Sion. In specimens from three cases, all of which showed evidences of repeated inflammatory change, the skin was found to be particularly thick, the epithelium desquamating, partially atrophic, and in all cases pigmented. In a fourth case there was merely atrophy with pigmentation. The most marked change found by this writer was a great increase in thickness of the epithelial layer. In the epiderm he observed isolated islets of parakeratosis in the interior of which were large masses of keratohyalin or pigment. The Malpighian layer was thickened and the inter-papillary epithelial bodies elongated. The granular layer contains an extraordinary amount of keratohyalin. Some of the epithelial cells stain faintly and in such cases usually exhibit degeneration of the nuclei and protoplasm, with complete breaking down of the cellular structures in some instances, —resulting here and there in the formation of veritable cavities.

The corium contains much cellular fibrous tissue, with here and there areas in which there are a small collection of cells. The elastic tissue everywhere presents itself as snake-like threads, which appear thicker than normal and degenerate. The blood vessels are dilated, the sweat glands hypertrophic, but the sebaceous glands normal. He found scarcely any plasma cells, and could demonstrate no change in the nerves. Where the skin has been subjected to repeated attacks it is found atrophic and strongly pigmented, with the horny layer of the epiderm thicker than normal, though not so marked as is the case in the more acute stages of the affection. In these chronic forms the Malpighian layer is thin and the papillary prolongations are either very broad and low or have entirely disappeared. The derma is atrophic, contains a few cells and some pigment.

Kozowsky (2) has found thickening of the corneous and Malpighian layers, and along with this the presence of a yellowish-brown pigment in the latter and between the different strata of the epiderm; he speaks of there being here and there small cavities filled with fluid and a small number of cell elements. The papillae are either normal or increased in size, and the lymph spaces are dilated, containing in addition to spindle-cells a considerable quantity of yellowish-brown pigment. While the writer says that the elastic fibers are on the whole intact, he still makes the assertion that they do not stain in the normal way with the usual reagents employed for this purpose. In the derma there is a marked increase in the number of cells around the blood vessels, the latter having hyaline walls. The cells encountered are lymphocytes and plasma cells, and here and there between the bundles of fibrous tissue connective tissue cells that appear to be larger than normal. Pigment is scattered throughout the entire skin between and often within the connective tissue cells, in the blood vessel walls, and in the lymph spaces; this pigment resembles that found in the epiderm. He states that the thick masses that stain bright-blue with methylene blue are probably degenerate elastic tissue fibrils. The nerve fibrils throughout stain feebly. Where the process is further advanced atrophic changes occur, the papillae are small and show hyaline change, and at the same time the epiderm is atrophied and contains less pigment. In the corium we see in such cases masses of cells, atrophy of the elastic fibers, pigmentary degeneration in the nerves, and hyaline change in the walls of the blood vessels. Often in the skin, at a distance from areas showing pellagraderms, the walls of the blood vessels here and there show hyaline change. On account of the pigment being scattered everywhere this writer thinks it is probably of blood origin; it resembles the pigment found in the nerve cells, but differs from it in not being colored dark by osmium. It contains no iron.

Recently Guard (2) has published a study of the changes that he found in the skin of pellagrins; he noted that the prickle and granular layers of the epiderm became thickened, and that there is degeneration of some of the tissues of the corium with collections of lymphoid and plasma cells, and an absence of mastcells and eosinophiles.

Fiocco (2) has written the best description of the acute changes so far published. He found in both epiderm and true skin considerable edema, affecting the sweat glands, the walls of the bloodvessels, and the walls of the nerves. In the epiderm and sweat glands the swelling is mainly intercellular, though in the Malpighian layer many cells are edematous, and ultimately degenerate and break down,—thus creating small blebs; similar collections of liquid also occur where the epiderm joins the derma. In the true skin there are edema, and small haemorrhages around the small vessels; there is, at least at first, little change in the elastin, but the fibrous tissue bands become swollen, and undergo degenerative changes, with the gradual formation of collacin. The endothelial cells of the blood vessels swell greatly, and often become almost occluded. Rarely a few polymorphonuclear leucocytes are found around the blood vessels. There are no plasma or giant cells. The only cellular elements found are mastcells and granule-bearing cells,—the latter being pigments derived from broken down red cells from the haemorrhages.

In the skin of old pellagrins the author has repeatedly discovered changes quite similar to those mentioned by Babes and Kozowsky, but which appear to have no relationship whatever to the acute process. He has found these changes where a history of acute pellagraderms was denied, and has seen them in a most pronounced fashion in the skin several years after a single acute pellagrous erythema had occurred.

The alteration consists in the gradual disappearance of both the collagenous and elastic tissues from the corium, the change extending deeper and deeper until finally, in some cases, the true skin is destroyed, with the exception only that there usually remains a thin layer of fibrous tissue forming the outer boundaries of the derma and supporting the epiderm. This layer, though usually somewhat thicker, reminds one of the similar stratum of normal dermal tissues which is always found lying in a similar situation in leprosy of the skin. In the areas of degeneration just referred to large fibres, which stain like elastic tissue, persist, though they are swollen, tortuous, and have acquired the property of taking basis dyes, including haematein; notwithstanding the fact that these structures have become basophilic they still stain beautifully by Weigert's method; when the change is far advanced they are decolorized in the author's regressive mordanting process for staining elastin. These masses, which are clearly what Unna calls "collacin," are usually found on section to be collected together in clumps, leaving around them wide open spaces which were evidently filled with fluids during life. It is possible that during the process of fixation a certain amount of shrinkage and agglutination of the tissues that remain may occur, but no one could look at these sections and not be impressed with the absolute necessity of there having been during life open, cyst-like areas scattered throughout the derma; this is further shown by the fact that on close inspection the spaces which had at first appeared empty are seen to contain more or less very finely granular material, which is occasionally arranged in such a fashion as to appear like very delicate, web-like structures. These areas of degeneration are not continuous throughout the corium, but form rounded or oblong, biscuit-shaped masses the long axes of which are parallel to the skin surface. In the central portions of these degenerate areas there are almost always found considerable numbers of mast cells, with here and there a polymorphonuclear leucocyte, and still more rarely an isolated lymphoid cell; around their periphery mast cells are again encountered, with a few lymph cells, and rarely a plasma cell. It is interesting to note that Unna (2) was unable to find plasma cells in the nearly related form of skin degeneration seen in the aged, nor were mast cells numerous (p. 983). The areas just mentioned are separated from each other usually by the ducts of the sweat glands, or by the sebaceous glands or hair follicles, and in many cases a small blood vessel clearly divides them. As many of the vessels show hyaline change, it seems extremely probable that these areas are the result of bad nutrition, coupled with the debilitating influences to which the skin of the hands is subjected, particularly in those who labor outdoors.

In this connection we should not lose sight of the fact, obviously overlooked by Babes and Sion (1), that the alterations just described are usually found in the habitually exposed skin of persons no longer young. The alteration was first described by Neumann, and was thought by him to be the result simply of old age, a view which was later shared by Schmidt. More recently Reizenstein showed that it may occur in relatively young people, he having found it in one person of twenty-six and another of twenty-eight years of age. In the same year Unna (1) showed that the lesion is probably the result of exposure to the inclemencies of the weather, as he found it largely confined to persons who labored in the open. Kryzysztalowicz has more recently written an interesting paper on the microchemic reactions of the altered tissues found in lesions of this kind. (See illustration).

While the author is fully in agreement with Unna as to the relatively greater frequency of this skin change in persons who labor out of doors, he would remark that it is certainly common in pellagrins and may occur in individuals who have spent their lives engaged in indoor occupations. There is, therefore, some justice in the assumption of Babes and Sion that this alteration has a close relationship to pellagra, though in all probability this is only a consequence of the gradual deterioration of health and the general tendency to senile change which is so marked in the unfortunate victims of this malady.

Up to the present time no one appears to have made a histologic study of the minor skin alterations which have been referred to in the chapter on symptomatology, and we are, therefore, not in a position to describe the changes that accompany them.

Thyroid.—The frequency of goitre and cretanism has long been a matter of common observation in those countries where pellagra prevails, but it is only within comparatively recent times that the matter has received the attention of pathologists. Valtorta (5) seems to have been the first observer to realize fully the significance of changes in the thyroid in connection with the clinical phenomena observed in this disease. More recently this organ has received a certain amount of attention where careful necropsies were being made; in some instances no alterations have been detected, as was the case in the investigations of O. Rossi, while Rubinato found most pronounced increase in the inter-lobular tissues. It is of extreme interest and importance to note the fact that Rondoni and Montagnani were able to produce profound alterations in this gland by feeding for a short time maize to animals.

Para-thyroids.—These glands appear to have received very little attention from pathologists working on this subject. Indeed, the only reference the author has been able to find was one contained in a recent article by O. Rossi, who mentions that careful examination failed to reveal any abnormalities of these glands.

Hypophysis.—The author has been able to find only one or two references to the hypophysis in his studies of the literature of pellagra. A few years since, in a most excellent article, O. Rossi mentions that a careful examination in one of his cases failed to show any lesions of this organ, but somewhat later Rubinato was able to find in one case that the cells of the anterior lobe of the gland were atrophic and much crowded together,—the change being most pronounced in the chromophilic cells; here and there cloudy swelling and necrobiosis of the glandular epithelium was observed.

Epiphysis.—As is in the case with the other glands of internal secretion, the pineal gland has received little or no attention from pathologists in connection with pellagra. The only investigator who seems to have given the matter any consideration is O. Rossi, who mentions that in one of his cases he was unable to discover any alteration in the gland.

Lesions of typhoid pellagra.—The pathologic alterations of so-called *typhoid pellagra* do not in any way differ from those encountered in the ordinary forms of the disease, with the exception only that intestinal lesions, especially in the large gut, are perhaps more apt to occur. Such being the case, no separate reference to this type of the disease would be considered necessary were it not for the fact that the term "typhoid" is more or less confusing, and implies a connection with a disease from which it evidently differs.

As would naturally be assumed, a clear distinction between typhoid fever and this form of pellagra is of a comparatively recent date,—there having been

a considerable amount of confusion regarding the matter among the pellagrologists of the last century.

The first writer who appears to have distinctly recognized the difference between typhoid fever and typhoid pellagra was Nardi (2), and some twenty-five years later this conception was placed on a firm basis by the investigations of A. Verga (3), who quite clearly showed that the lesions in the two diseases have little or no resemblance. Since that time a number of investigators have given the matter consideration, and have quite uniformly confirmed the previous investigations of Verga. Among these may be mentioned Foà (2), Venturi, Morselli, Belmondo (1, 2), Vassale, Sacconaghi, and O. Rossi. While it is true, as shown by Venturi, that the adenoid tissues of the intestines and abdominal cavity sometimes become swollen in this form of pellagra, we do not find, as in typhoid fever, marked lesions of Peyer's patches, and a greatly enlarged spleen; furthermore, the specific organisms are absent from the blood.

Pathologic alterations in hereditary pellagra.—Unfortunately little has been done in this most important matter. Simonini seems to have made the only necropsies thus far reported.

In one, a child of eight, who had hydrocepalus, and a chronic leptomeningitis, he found closure of the faromen of Majendie, inflammation of the charoid plexuses, and leptemingitis; in another, who had *paraplegia spasmodica congenita,* there were evidences of chronic meningitis, and miscroscopically he found scarcity of the nerves cells of the cord, with alteration in their form and size, an equal diminution of the nerve fibres of the white substance, and in the pyramidal tracts of the cervical region there were areas of sclerosis, and similar changes in the columns of Goll. There were no other changes of importance.

General conslusions.—Summing up the alterations to which attention has been called in the preceding pages, we find that pellagra is characterized by a widespread degeneration of the walls of the smaller blood vessels, marked changes of both acute and chronic character in the brain, cerebellum and spinal cord, together with lesions, usually of less severity, in the various ganglia, and peripheral nervous system, periodic acute pathologic processes in the skin, with chronic lesions of the corium in certain situations, alteration in the parenchymatous elements of the liver, kidneys and adrenals, changes in the heart muscle, softening of the bones and general passive congestion of the body. As to just how far these lesions are due to the pathogenic agencies that produce the disease in the beginning, and to precisely what extent they are caused by the altered metabolism that results from the primary changes we are unfortunately not in a position to determine; we can only say that it is highly probable that many of the alterations are of a secondary character.

On account of their widespread character and their evident relationship to many of the clinical phenomena observed, none of the alterations that have been discovered in this malady perhaps exceed in importance the changes found in the smaller blood vessels; in addition to these, atheromatous processes occur in the larger blood vessels occasionally, though these alterations are probably usually secondary to change in the vasa vasorum, and are by no means constant.

As pointed out by Kozowsky, we have here changes corresponding to the two varieties of arterio-sclerosis recognized by Jores,—these being called by him "hyperplastic thickening of the intima" and "regenerative connective tissue hyperplasis of the intima" respectively. The former alteration is characterized by a longitudinal splitting of the internal elastic lamina, which process may be repeated over and over again until the intima of the vessel is greatly increased in thickness; this process is regarded as being, in a measure at least, physiological, which makes its first appearance in childhood and gradually increases with age. The second form results in thickening of the intima as a consequence of the production of a ground substance of connective tissue, in which there are formed many new elastic tissue fibrils,—the internal elastic lamina remaining normal. In connection with this form of arterio-sclerosis there are always evidences of proliferation in the other coats of the blood vessels. This latter process is found only in the very smallest blood vessels, the anatomic alterations in the diseased vessels approaching closely to the arterio-capillary fibrosis of Gull and Sutton. Kozowsky has also particularly called attention to other changes in the smaller bood vessels, this author finding in addition to the connective tissue hyperplasia of

the intima, hyaline alterations in the other coats, and now and then regenerative processes in the adventitia. As to the cause of alterations of this character authors are now pretty well in accord, it being generally conceded that the ordinary form of arterio-sclerosis is the result of a chronic intoxication, the poisons probably ordinarily resulting from disturbances of digestion or errors in metabolism, and in some special cases may be unquestionably the consequence of exogenous mineral poisonings, such as those produced by lead. As respects the hyaline change, this alteration also is regarded by all writers as being the consequence of toxines circulating in the body fluids.

Ribbert says, "Hyaline degeneration is more simply explained by supposing a local disturbance of catabolism" (p. 222).

Tarassewitsch says, "Hyaline degeneration develops mainly in chronic infections and from poisons such as syphilis and alcohol" (p. 100).

Podwyssozky says, "The causes of hyaline degeneration of the connective tissues are not the same in all cases. In the overwhelming majority of instances such regional tumefaction and modification of the connective tissues are provoked by all conditions that make slow and bad their nutrition, oxygen hunger, and apparently also by such agencies as act as poisons" (p. 86).

Reprew says, "Hyaline is produced as the result of various conditions and influences. Among these are toxines in general and plasmatic poisons, which produce a metamorphosis of the blood into hyaline masses. In other words, under the influence of poisonous substances, which work with some degree of energy, necrobiosis is provoked, with destruction of the living protoplasm; then begins the chemical transformation of the altered protoplasm into substances that belong to the group of heteroglobulins, which in turn is changed into what is called extra-cellular hyaline" (p. 27).

Ziegler says that "The lesion is produced partially by local and partially by general disturbances of nutrition (p. 228).

Martin says that "The most important cause of cell and tissue degeneration is the circulation of a poison in the body, and such poisons may produce a widespread degeneration" (p. 193).

From the foregoing we may assume with Kozowsky that hyaline degeneration of the blood vessels is produced by poisons which circulate in the blood for a long time, resulting in decreased catabolism, anaemia, and lastly sclerotic and other changes in the organs supplies by these vessels. It may be remarked that these alterations are most common in the spleen, liver, kidneys, and brain. Kozowsky observed purely local areas of arterio-sclerosis,—this process being found occasionally in the lungs and other tissues.

The alterations that occur in the central nervous system are likewise of such character as would lead us immediately to associate them with a chronic intoxication,—the nerve cells being evidently particularly susceptible; the areas of softening, with the production of cavities, and the sclerosis may be in a measure accounted for by the changes in the blood vessels. Kozowsky calls attention to the fact that the arterio-sclerosis observed by him in the nervous system in pellagra closely resembles that to which a number of authors have called attention as occurring in old age, and to which Nonne and Luce have devoted a special chapter in their article on the pathological anatomy of the blood vessels in brain diseases in Flatau's Handbook of the Pathological Anatomy of the Nervous System (Bd. 1, pp. 272-301). In both instances there are found a sclerosis of the small vessels, with destruction of their lumina and development of connective tissue in their adventitiae, followed by degeneration of the nerve fibers; it is noteworthy that these alterations are more pronounced around the edge of the cord than is the case in senility. The system scleroses in the white substance are undoubtedly the result of the destruction of the nerve cells of the brain, followed by degenerative changes in their axons. The character of the foregoing changes in the nervous system is such that all must agree with Kozowsky that the alteration cannot be simply an ordinary purely senile arterio-sclerotic process, but one that is very complicated, and to be explained only by the peculiarities of the poison producing it. It cannot, for example, be the case that the cavities found in the gray matter of the spinal cord are the consequence of a simple arterio-sclerosis, though the presence in them of the remains of blood vessels and blood cells shows that they have some connection with these structures. It seems not

unlikely that the softened areas are the result of hemorrhage, as it is well-known that such changes occur in other parts of the central nervous system, as, for example, in the brain; whether this is the result of thrombosis cannot be at present determined. It is likewise true that a simple change of this kind in the blood vessels would not be followed by cysts in the brain substance.

The changes that occur in the nerve cells resemble somewhat those that result from senility, particularly as regards the degree of pigmentation, but still there are marked differences. That these alterations may be in a measure brought about by poor circulation is not impossible, but the widespread nature of the change and the very peculiar and characteristic lesions that occur indicate clearly that other agencies are at work. When the cells in the motor cortex degenerate we naturally have corresponding changes in the pyramidal tracts, but this does not explain the similar alterations which have been found by Rossi, Babes, Gregor, Kozowsky, and many others, in the purely sensory columns of the spinal cord, and which of necessity must be of exogenous origin,—thus doing away with the theory of Marie, according to which the changes in this malady are always initiated within the central nervous system. As was first shown by Dejerine, and later by Rossi, Babes and Kozowsky, the cutaneous nerves frequently show more or less alteration. In this connection we should not forget the profound alterations that occur in the spinal and sympathetic ganglia, all of which together clearly indicate the action of some toxic substance, as these changes could by no possible stretch of the imagination be considered as entirely due to arterio-sclerosis, and the total lack of all acute so-called inflammatory phenomena makes it in the highest degree improbable that the changes could be a consequence of infection. It is interesting to note in this connection that Schtscherbak has reported a case of lobster poisoning in which there was degeneration of the nerve endings.

Neither can it be assumed that the alterations in the neuroglia are the simple consequence of arterio-sclerosis. Kozowsky admits the possibility of changes in the neuroglia without other alteration, as would be indicated by the works of Chasslin, Anglade and Choereaux, Marchand, Elmiger and Alzheimer, notwithstanding which this writer is entirely of the opinion that the increase in neuroglia elements in pellagra is altogether secondary; this opinion is based upon the fact that the alterations seem clearly of a reparative character, the occurrence of such changes in the neighborhood of degenerate nerve elements, and from the fact that nowhere has he found that peculiar variety of lesion which is characteristic of inflammatory processes in the central nervous system; lastly it may be mentioned that arterio-sclerotic alteration could not alone cause the occasional presence of lymphocytes about the blood vessels, marked thickening of the brain coverings, and compression of the posterior roots.

The obliteration of the central canal of the cord is of no consequence, inasmuch as it is often observed in normal individuals.

The presence in the liver of quantities of brown pigment along with fatty infiltration and degeneration, as well as the occasional presence of albuminoid degeneration, altogether point toward some toxine circulating in the blood. As to the origin of the hypertrophy of the connective tissue and the occasional increase in bile ducts nothing can be definitely concluded. Many writers have regarded simple passive congestion as a possible source of cirrhotic conditions of this organ, and certainly, if this be the case. the dilitation of the central vein with the increased blood in the organ in pellagra, clearly points to a possible solution of the cause of the process. On the other hand it is held by many that cirrhotic conditions are secondary to degenerative changes in the parenchyma of the organ, and as we have here pronounced degenerative alterations in the liver cells this hypothesis easily accounts for the increase in connective tissue observed. It is, of course, easy to assume with Huchard that the cirrhotic conditions are the result of a decrease in the calibre of the smaller blood vessels and the consequent anaemia and degeneration of the parenchyma of the organ, but as to how far this explanation is true in the present instance we have unfortunately no data from which to determine.

Finally, we can only say that there is every evidence of a poison, and that this substance in some manner produces degeneration of the liver cells and at a later time cirrhosis.

In the spleen we find evidences of both atrophic and hypertrophic processes, and, when we remember that the organ is virtually one huge blood vessel, it is easy to understand that any toxine that may be present would naturally produce here most profound alterations. The walls of the blood vessels are thickened, and their lumina are often obliterated by a hyaline swelling of the intima,—which change likewise may be extended to the other coats. The veins are enlarged and filled with blood. The connective tissues are markedly increased, and produce a gradual contraction of the organ. The cell-elements of the spleen in some cases are increased, though as a rule they are diminished. A like remark holds as regards the follicles. These alterations could scarcely be accounted for in any other way than by the presence of a toxine.

In the kidneys the changes observed are thickening of the internal coats of the blood vessels and of Bowman's capsule, along with more or less degenerative change in the tubules. The cirrhotic alterations correspond to those that occur in congestion of the kidney, differing from the typical arterio-sclerosis in that the glomerules are intact. The destruction of the parenchymatous tissue can only be accounted for by the action of a poison.

In the adrenals more or less change is constant. Whether these alterations are due to arterio-sclerosis, or to the direct action of the poison is not clear.

No characteristic changes in the pancreas are found.

The heart shows brown atrophy, with interstitial increase of its fibrous tissue,—the latter change occurring not only around the blood vessels, but in all parts of the viscus. It is likewise true that the nervous structures of the heart show alteration. It is hardly likely that these changes are the result of the arterio-sclerotic condition, but like the majority of those occurring in the other viscera it is doubtless the consequence of a circulating poison.

In the gastrointestinal tract there are found chronic catarrh, with later localized atrophies. These alterations may be perhaps in a measure the result of the general venous congestion, and to a certain extent of the arterio-sclerotic changes, and, probably even to a still greater degree, of the pellagrous poison. If the other tissues of epidermal origin were not universally diseased one might be disposed to consider the possibility of the gastrointestinal changes being the result of the action of local irritants, but the widespread nature of the process would seem to contradict this view. It is, however, likely in all cases that the ulcerative processes in every part of the tract are the consequences of the action of bacterial toxines, which would be ordinarily harmless, but which, acting on the already diseased tissues, exert an increased toxic affect. Kozowsky mentions the work of Cowen on inflammations of the intestines in the insane, and notes that he came to the conclusion that these conditions have as their basis degenerative changes in the nervous system.

The lungs show no marked change, though there are commonly found scattered throughout their substance small areas of peribronchitis, accompanied by more or less arterio-sclerosis.

The bones usually show marked alteration, consisting of rarefication as the result of the action of osteoclasts and of halisteresis.

The alterations in the skin may be distinctly classed into two groups. The more important of these consists in the lesions which are generally regarded as being the most characteristic symptom of pellagra; such alterations are undoubtedly largely the result of the action of irritants, notably light, on a tissue of lowered resistance. These lesions may also follow immediately in the wake of chemical irritation, and may have their beginning in bacterial infection. They are probably also greatly influenced by altered innervation.

The other change is one that is unquestionably due either to changes in the blood vessel, or to the direct action of the poison, combined with the influences which would in the natural course of events produce lowered resistance in the skin covering exposed parts of the body. How far each of these agencies acts it is impossible to say. The pigment which is abundantly observed in the skin is thought by Kozowsky to be of haematogenous origin.

The lymph nodes show cirrhotic processes, with decrease of parenchymatous elements and an increase of pigment.

Finally, we may summarize the pathological changes as follows:

Pellagra is a chronic disease, with occasional acute exacerbations, and is anatomically characterized by physical evidences of degeneration, by dysplasias in the spinal cord, by lesions of the walls of the finer blood vessels, by changes throughout the entire nervous system, by productive processes in the various viscera, accompanied by acute, so-called inflammatory conditions of the skin and mucous membrances, and degenerative changes which are particularly marked and characteristic in the nervous system and the derma.

A study of the lesions would be to a large degree futile in bringing us to a proper conception of this malady should we fail to appreciate the capital significance of their extreme chronicity. While this has been in a measure understood even from the time of Strambio, and was particularly insisted upon by Roussell in some aspects of the question, it appears to the author that most of the misunderstandings and errors that have arisen in the past respecting this disease are the consequence of a failure to appreciate the great importance of this fact. The anatomic alterations are probably to a certain extent congenital, and those that are acquired are undoubtedly produced gradually and in sequence, and only become pronounced after the lapse of many years. The lesions which together cause the characteristic morbid picture are of a permanent character, and having been once initiated remain and probably slowly increase throughout life, impairing eventually the functional capacity of the parenchymatous organs of the body, and producing a gradual and more or less steady decline in the general health. Such a conception would assign to the external and manifest alterations a wholly unimportant and insignificant rôle, notwithstanding their importance from a clinical standpoint; in truth it may be advantageously assumed that the acute lesions of the skin and gastrointestinal tract are of an almost accidental character, and the result of external and wholly extraneous agencies acting upon the chronically diseased tissues, the resistance of which is particularly decreased at certain seasons. Such a view explains the well-known increase in pellagra which results from misery; it shows that the affection must necessarily be of an intractable nature; it indicates why it is that patients frequently develop the external symptoms years after ceasing to eat maize products, and does away with the necessity of assuming an acute intoxication, which, it appears to the author, has been the stumbling-block in the pathway of a proper conception of this malady, the many objections to which have been frequently pointed out as an unanswerable argument against the maize theory of its causation; on the other hand, finally, it does not deny the possibility of the influence of the mould poisons of Indian corn as occasional, or even frequent, determining factors in the production of the acute outbreaks of the classic symptoms.

PATHOLOGIC DIAGNOSIS:—While it may possibly be true, as maintained by Singer and Pollock, that, in the present state of knowledge, we can not differentiate with certainty the lesions produced by pellagra in the nervous system from pathologic states resulting from other morbific influences, there can be little doubt that this desirable end will be fully accomplished at a no very distant date; in the meantime probably no one would deny that a thorough study of all of the pathologic alterations in any given case could only in very rare instances fail to make their true character clear. It should not be forgotten, however, that Kozowsky, by far the most thorough and careful of those who have worked on this subject, by no means agrees with the opinion of the authors just quoted,—he regarding the lesions as being quite characteristic, as does also Marinesco. The points in the differential diagnosis that follow have been largely taken from Kozowsky's monograph.

Anatomically the changes of pellagra may be mistaken for those occurring in the following conditions:

(1) *Senility.* The fact that pellagrins become prematurely senile was long ago recognized by Sacchi, G. B. Verga (1), and Lombroso (11), but it remained for Foà (1) first fully to perceive the general nature of the process, and to enunciate its extent and significance in the following remarkable words:

"Also in the ganglia, as in all the other organs, we find signs of precocious senility, such as may be caused by chronic poisoning, from which may be derived second-hand, many of those symptoms of altered innervation of the viscera which characterize the course of some forms of pellagra" (pp. 277-278).

Still later this connection was discussed more fully by Alpago-Novello (2), but it is unquestionably the great merit of Kozowsky (2) to have insisted on the close relationship that exists between the two from a pathological standpoint. It is interesting to note that the theories which at present prevail respecting the causation of old age all assume that senility is the result of some kind of auto-intoxication; thus Kassowitz maintains that old age is brought about by the increase of certain products of cell metabolism; Maly believes that both senility and marasmus are the result of a chronic autointoxication, and Metchnikow holds to the same opinion, differing only with these writers as to the origin of the poison. The pathological changes in the two are so similar that Kozowsky says that they may be differentiated only with extreme difficulty in advancing years, though as a rule by taking into consideration all data obtainable the differential diagnosis may be made. Should it be proved that senility is in any considerable degree due to a chronic autointoxication, the facts adduced in this brochure concerning the transmission of the effects of such influences from parent to offspring would lead to the assumption that where toxic processes are particularly pronounced in the former the latter would come into the world handicapped by lowered vitality and unhealthy organs and tissues, and would perish earlier than those with a normal ancestry,—a fact borne out by every-day experience; such a state of affairs would furnish a clear explanation of the close relationship of old age to pellagra.

In old age the *heart* is large, in pellagra it is usually small. The *larger blood vessels* are frequently diseased in the former condition, while the *smaller* are only notably affected in the latter.

The *kidneys* in senility show arterio-sclerotic alteration, while in pellagra they present the changes that result from cyanotic induration. In both conditions there is found an increase of the fibrous structures of the *liver*, and the organ may present the well-known nutmeg appearance, but in pellagra the arterio-sclerosis is less intense.

In old age the *spleen* is usually smaller than normal, the capsule thickened and white, and the substance soft, though in some instances it is larger than normal; similar changes may be found in pellagra.

In old age we see *alveolar emphysema*, along with *catarrh* and *atrophic changes* in the mucosa of the *bronchi*, while in pellagra there are often found here and there areas of peribronchial pneumonia after death.

In the *nervous system* we find changes in pellagra which in many respects resemble those observed in old age, such alterations being thickening of the meninges, pigmentation of the nerve cells, sclerosis of the tissues of the central nervous system, and in the brain the so-called "état criblé;" in both we likewise find alterations of the blood vessels, but they differ markedly in character, those found in old age showing typical arterio-sclerosis, while in pellagra, in addition to slight changes of a similar kind, we have hyaline degeneration of the inner and middle coats, with the formation of much fat, all clearly indicating profound degenerative alterations. It is also of importance to observe that a number of writers have remarked that the deeply lying tangential fibers of the cerebral cortex undergo degenerative changes in senility, while on the other hand it is only those which are superfically situated that show similar alteration in pellagra. It is worthy of especial note that both Marinesco and Rezza consider the peculiar hyaline change in the nerve cells in pellagra as being quite characteristic. In the center of the cells that show this hyaline alteration in a pronounced fashion the neurofibrils fail to take the stain, in which particular the cells again differ from those showing alteration in old age. It is of extreme interest to note that Rezza reports in one case typical *Fischer's plaques* in a pellagrous individual sixty-six years of age; these peculiar bodies have been heretofore considered characteristic of senile dementia, and their discovery in connection with this disease is most important. Mitotic figures in the cells of the brain are likewise occasionally seen in pellagra, though not in old age. Of very great importance is the fact that throughout the brain substance in senility pronounced fatty alterations are everywhere encountered; similar changes are also observed in pellagra, but by no means to so marked a degree.

The two conditions likewise show some resemblance in the character of the lesions of the *cord*. In senility we find marked arterio-sclerosis, atrophy of the

ganglion cells of the anterior horns, many corpora amylacea, and pigmentation of the nerve cells, and sometimes disseminated sclerosis; in pellagra on the other hand we find the changes in the blood vessels of a different characted, advanced degeneration in the cells of Clarke's column, and scleroses in the pyramidal tracts and posterior columns.

It is also of importance to note that the *peripheral nerves* suffer more or less in pellagra, which is not the case in senility.

In the earlier stages of *senile dementia* the character of the alterations in the brain approach quite closely to those observed in pellagra. In the variety of the former condition which is associated with *arterio-sclerosis* we have the brain enlarged, the blood vessels markedly sclerotic, the white substance tough, with gray streaks running through it, and the ventricles widely dilated. In the form characterized by *chronic subcortical encephalitis* the white substance is rarefied, the ventricles enlarged, but the cortical substance remains normal.

In the cord we find in these forms of *early dementia*, particularly around the vessels, which are greatly altered, many spider cells, and, in addition, points of softening. In *subcortical encephalitis* the gray substance of the cord shows enormous numbers of granular cells. It is of interest to note that Bravetta (1) has observed in the nerve cells of those dying of pellagra swelling of the neurofibrils, a condition evidently closely approaching to the change in these cells first described by Alzheimer, and which has heretofore been generally regarded as characteristic of senile dementia. The close relationship of senile dementia and pellagra is likewise shown by the frequent discovery in the brains of those dying of the latter disease of Robertson's cencentric bodies, and in one case of Fischer's plaques by Rezza.

It is furthermore true that the brain in senility is typically atrophic, this being evidenced by a marked shrinkage of the convolutions, edema of the telae choroideae, and a great abundance of cerebrospinal fluid on opening the cranium. *Local hemorrhages* are likewise common to both, this being quite apparent to the naked eye in old age, but almost always microscopic in pellagra. It may also be noted that in old age there is atrophy of the intestinal walls, while in pellagra, in addition to alteration of this character, we usually have inflammatory processes and often ulceration. The skin likewise shows alterations both in senility and in pellagra, but in the latter condition the microscopic changes that occur differ widely from those found in the former; while in old age the change begins in the elastic fibrils of the outermost layers and gradually proceeds deeper and deeper into the substance of the skin, in pellagra the changes begin in the fibrous tissue, causing its complete disappearance, and leaving masses of collacin and elastic tissue

The author is indebted to Friedmann's excellent monograph on senility for the greater portion of the data on the pathologic alterations that occur in this condition.

(2) *Progressive paralysis. Progressive paralysis* and *pellagrous insanity* frequently show symptoms which so closely resemble each other that some confusion has existed respecting them in the minds of alienists for the last 50 or 60 years. Owing to the researches of Alzheimer it is, however, now quite certain that the two affections may be differentiated histologically, which is of much importance, particularly in those cases where general paralysis is accompanied by a dermatitis of the hands. In general paralysis we have enormous collections of plasma cells around the finer blood vessels of the brain, which would alone serve to differentiate this condition from pellagra; when we further take into consideration the marked atheromatous changes of the larger blood vessels, the fatty degeneration of the liver, kidneys and heart muscle so common in this affection, the distinction between the two becomes even more clear.

(3) *Chronic alcoholism.* The changes in the nervous system in *chronic alcoholism* and in pellagra show certain points of resemblance, there being in both marked destruction of nerve cells, often preceded by the formation of vacuoles and fatty degeneration, and cellular infiltration into the meninges; this resemblance holds both in the brain and in the cord. There are, however, certain points of non-resemblance, it being true that in alcoholism the nerve cells do not exhibit that peculiar hyaline change which is so often encountered in pellagra, nor are the other alterations so marked or of so varied a character; according to

Marinesco (Vol. II., p. 320) the changes in the former are scarcely noticeable in the Ammon's horn, and Braun's (p. 92) description of the changes in the nerve cell in experimental alcoholism in animals shows that they almost wholly belong to the type of direct cell reactions. Furthermore there is no pronounced cellular infiltration around the blood vessels in alcoholism, a fact to which Cramer particularly called attention, nor is there the marked gliosis in the cerebellum which is so characteristic of pellagra. In both conditions there is more or less inflammatory condition of the peripheral nerves, but this is in the great majority of instances far more marked in alcoholism than in pellagra. Fatty alterations of all the internal organs is likewise the rule in alcoholic poisonings, while it is rare in pellagra. It is noteworthy too that pigmentary changes are not present in alcoholism.

(4) *Syphilitic alteration.—Syphilitic alterations* could hardly be mistaken for changes that occur in pellagra. In the former we have an energetic cell multiplication in the walls of the blood vessels, with rapid destruction of the cell-elements and nerve fibers, and numerous points of softening; there is likewise in all of the older forms marked arterio-sclerosis.

(5) *Ergotism.* As shown by Winogradow, the changes in *ergotism* closely resemble those that occur in pellagra, but in the parenchymatous organs the inflammatory process and haemorrhages are more pronounced in the former, and likewise Zinker's degeneration of the heart muscle fibers occurs. Furthermore, in this condition there is a marked degeneration of the posterior nerve roots and posterior columns, while the anterior horns remain unaffected; Lissauer's zone is likewise intact according to Tuczek (1). In pellagra it is principally the pyramidal tracts which are affected, though the posterior columns and Lissauer's zone not infrequently show degenerative change.

(6) *Lathyrismus.* Unfortunately the literature on the morbid anatomy of *lathyrismus* is very sparse. The symptoms would lead to the conclusion that the principal lesion is a transverse myelitis in the dorsal region. Holzinger is of the opinion that the anatomical changes are only temporary, but this is hardly in keeping with the results of clinical observation. An exceedingly interesting article on this subject is one published by Kirk in 1860-1861, which deals with the effects produced by the use of leguminous seed commonly eaten in India as articles of food. The writer mentions that the continued eating of food of this character results in complete paralysis of the lower limbs, which lasts for life. An equally instructive article was written by Astier on observations made by him in northern Africa on this affection. He likewise speaks of permanent paralysis, with contractures of the lower limbs, accompanied by increased kneejerk and in some instances disturbances of sensibility, though this is not uniform. A thorough study of the pathologic alterations that occur in this affection is highly desirable.

(7) *Beri-Beri.* In this disease it has been long known that the principal lesions consist in a general and profound inflammation of the nerves. In a very thorough study of the subject recently made by Dürck, he found haemorrhages in the gray substance of the cord, tygrolysis in the nerve cells of the anterior and lateral horns, and in Clarke's column. There were also scleroses of the posterior columns of the cord, especially in the columns of Goll. These changes are found at all levels, and of course resemble those of pellagra very slightly.

(8) *Acrodynia.* This disease, which is generally believed to be the result of eating food products made from decomposing wheat, is in some particulars like pellagra. We have in both derangements of the digestive tract and erythema of the extremities, together with sensory disturbances. The process is much more acute than pellagra. The affection, when the patient recovers, is followed by great feebleness and paralysis. Unfortunately we are in complete ignorance of the pathological anatomy of this condition, but that the central nervous system is affected can not be doubted.

(9) *Addison's disease.* The adrenals, which commonly show morbid change in Addison's disease, may likewise exhibit alteration in pellagra, as is shown by the extremely interesting investigations of Finotti and Tedeschi. We do not have in simple Addison's disease, however, changes in the central nervous system, which easily distinguishes between the two maladies.

(10) *Sclerosis of the cord from other toxic blood states.* That toxic blood states not uncommonly give rise to sclerotic changes in the central nervous system

has long been known. Thus we find, as shown by Tuczek (1), that alterations of this kind are very frequent in ergotism. Likewise changes of a similar character are by no means infrequent in profound anaemias, as was first noted by Lichtheim (1, 2), and later confirmed by Minnich (1, 2), Van Noorden, Nonne, Bowman, Taylor, Bastianelli, Clarke, Burr, and many others. Williamson has also shown that sclerotic changes are occasionally found in the cord in diabetes, and, of very great interest to us in this connection, similar alterations have been described by Putnam in the aged and enfeebled, and by Campbell in the aged insane. Some years ago the author examined the cords in two cases of what appeared to be pernicious anaemia, and found alterations in both; however, in view of later experience, it appears not impossible that these patients may have been the victims of that not uncommon type of pellagra that is chiefly characterized by profound anaemia. Gowers, in his masterly manner, has recently discussed, in his well-known text book on nervous diseases, six cases of pernicious anaemia in which lesions of the cord were found after death, and states that there is little room to doubt that the sclerotic condition was the result of a toxic state of the blood, though the nature of the poison he admits is unknown. That writer regards the change as being probably in the nature of a parenchymatous degeneration of the nerve-substance, with secondary overgrowth and hardening of the connective tissues.

The changes in the cord are, as Gowers states, curiously uniform, being widespread in the cervical region, and occurring in the anterior, lateral and posterior columns; in the dorsal region the change is still extensive, but there is a gradual diminution downward, so that in the lumbar region the sclerosis is much less widespread and less complete in character. It is interesting to note that the septo-marginal and cornu commissurale tracts, which are both probably of endogenous origin, are spared in the lumbar region, and at the same time the pyramidal tracts in this area only show disease in a restricted area close to the posterior roots. But little change occurs in the anterior horns or Clarke's column, thus sharply differentiating the cord changes from those that occur in pellagra. It may also be mentioned that the arteries are generally found in a state of advanced sclerosis in these anomalous cord diseases. So far as is known no changes occur in the brain itself, though that such alterations take place is highly probable.

In conditions of extreme inanition there are frequently found congestion of the viscera, acute hepatitis, interstitial inflammations of the kidney, and atrophy of the nerve cells as will as simular changes in the heart, the liver, the kidneys and the muscles. Tarassewitsch and Schestnow found in long-continued inanition pigmentation, hayaline degeneration of the connective tissues, brown atrophy, and other changes, all of which somewhat reminds us of pellagra, though rarely closely simulating it.

CHAPTER IV

SYMPTOMATOLOGY.

The symptomatology of pellagra is as complex as its morbid anatomy. The changes in the skin, the disturbances in the alimentary canal, and the mental alienation together constitute the trinity of classical symptoms of constant and far advanced alterations in the entire body, particularly in the central nervous system, and the author believes only occur after irreparable damage has taken place. It, therefore, follows that where recognition of the disease is delayed until these manifestations appear little can be done for the unfortunate sufferer in the great majority of instances. While it is true that patients generally recover from the first few attacks of the external manifestations of the affection the tendency is gradually to grow worse with each succeeding onset, and death finally ends the melancholy scene, despite the use of any or all of the so-called cures.

Accepting the foregoing as being true the question naturally arises as to whether it be possible to recognize the malady at a sufficiently early stage to permit the successful application of appropriate prophylactic remedies? In reply the author has no hesitation in saying that pellagra may be probably in all instances diagnosticated many years before the development of the classical symptoms, and, while it is perhaps not yet possible to speak with certainty as to our ability to curb further pathological alterations in the body, the results of clinical experience would indicate that in many instances this is entirely feasible. More constant and scarcely less striking than the classical symptoms of the fully developed disease are the clinical phenomena that invariably precede—usually by many years—the typical outbreaks of the malady, and when taken together constitute a picture, in the vast majority of instances, that cannot be mistaken. These earlier manifestations have been in a measure known since the time of Casal, and it is indeed singular that their significance has not been more fully recognized, since they are referred to by all systematic writers on this subject. This is doubtless a result of the fact that *they have been only regarded as the prodromal symptoms that usher in a typical pellagrous onset,*—this attitude on the part of pellagrologists being fostered by the clearly erroneous view that each external outbreak is preceded by a definite maize poisoning.

In their clinical portrayals students of this subject have as a rule attempted to divide the malady into various stages or degrees,—such divisions having as their basis either convenience of description, or, more commonly, the preconceived notions of their proponents respecting the etiology and morbid changes that occur in this affection.

Thus we find that while Strambio (4) divides the malady into the *intermittent, remittent* and *continuous,* Gherardini recognizes *mild, severe, grave* and *complicated forms* of the disease. These classifications are extremely satisfactory, and are superior to the great majority of those that have been since devised,—having the great merit that they rest on no unproved assumptions, while at the same time they offer excellent opportunities for a satisfactory division of the clinical phenomena.

Soler distinguished a *humid* and *dry form* of the malady, this depending on the degree of superficial moisture present in the lesions, —which condition he believed to be largely influenced by the character of the climate.

Titius recognized an *occult* and *manifest form* of the malady.

Jansen described *incipient, confirmed* and *desperate varieties,* while Cerri first introduced the idea of definite stages, recognizing a *first, second* and *third degree* of the disease.

Morelli divides the affection into the *eruptive,* the *nervous,* and the *colliquative forms,* failing entirely to recognize the earlier stages.

Lussana and Frua divided pellagra into *five stages,* as follows:

(1) Weakness, vertigo and nervous symptoms (mal del padrone).

(2) Mental hebetude and melancholy.

(3) Pellagrous mania.

(4) Dementia and wasting away of the body.

(5) Typhoid pellagra.

Like a majority of the earlier classifications that of Roussel (3) is faulty, since it is based on a purely speculative correspondence between the clinical phenomena and the supposed degree of poisoning on the one hand, and an assumed varying extent of pathologic alteration on the other. The ordinary pellagra he divides into two groups, which he respectively calls pellagra of the *first* and *second degrees:* pellagra of the first degree is further subdivided into *commencing* pellagra and *confirmed* pellagra. Both of these stages of the disease he regards as the direct result of the toxic action of poisons.

In addition he recognizes two other stages of the malady, both characterized by *cachexia* and differing only in that one (a) presents *obvious skin alterations,* while the other (b) *is free from such manifestations.*

(a) This form is regarded as a stage of the malady which might be equally well called the third degree, and is characterized, [illegible]ding to this author's view, by permanent tissue changes which [illegible]anism is no longer able to repair in the intervals between [illegible]cks, and as a consequence the patient never again entirely re- [illegible] such patients present in addition to the occasional typical

erythemas frequent *purpuric spots,* and *extreme dryness* and *roughness of the skin.*

(b) This form of the disease Roussel regards as a stage occasionally reached where the patient, having given up maize products, no longer suffers from their direct effects, but whose organs are so damaged by previous attacks that a chronic cachetic condition develops which is distinguished from the similar state just considered by the absence of active skin symptoms.

We thus find that the classification proposed by this eminent pellagrologist is based upon theoretical considerations which not even the great advances of modern times could justify, and which in a measure appear to be directly contradicted by our studies in pathological histology.

We should, however, not fail to point out in this connection that Roussel appears to have been the first pellagrologist to recognize that irreparable organic changes must occur where pellagra is long-continued,—a conception which is all the more remarkable in that no positive data existed in his day indicating such a possibility; indeed, this investigator appears even up to the present tme to be the only writer who has attributed definite clinical forms of pellagra to corresponding pathologic changes in the body.

The French writers have generally accepted Roussel's classification, and we find Procopiu, Poussié and others adopting the division suggested by this great pellagrologist.

A much more recent classification is that of the celebrated Italian clinician Devoto (1), who divides the malady into the following varieties:

(1) The beginning form.

(2) The mild form (with circumscribed functional alterations).

(3) The moderately severe form (with functional alterations of divers organs).

(4) The grave form (with structural alterations of one or more organs).

This classification might be useful simply as an arbitrary division of the symptomatology of the disease did it not unfortunately attempt to correlate these manifestations with purely supposititious stages in pathological alteration. As a matter of fact there are many reasons going to show that the symptoms do not manifest themselves until structural alteration in one or more organs has already occurred, and it does not, therefore, appear that this attempted division of the symptoms of pellagra is justified in the present stage of knowledge.

Another recent classification is that of the celebrated Roumanian pellagrologists Babes and Sion (2), who recognized:

(1) A prodomal, or, better, a pre-erythematous stage.

(2) An erythematous stage, with stomach and intestinal disturbances, along with less marked general and peripheral nervous manifestations.

(3) A stage in which there are nervous symptoms consisting of mania, particularly hydromania, delirium, convulsions, contractures, and general weakness. And finally,

(4) A stage in which there is deepest depression, melancholy, imbecility, paralyses, diarrhoea, and cachexia.

These writers remark, however, that the foregoing stages are not to be regarded as sharply defined, since cases occur even in the first stages in which there are mania, colicky diarrhoeas, and cachexia, while on the other hand many patients show no further development of the malady, even in from five to ten years.

Other writers, such as Neusser (1), Lombroso (11), and A. Marie (2) make no attempt at a division of symptoms in pellagra.

The question as to whether such a division is advisable is purely one of convenience, since there are no clear and distinct lines of demarcation between the various stages exhibited by this disease other than a period, usually covering many years, during which the symptoms are mild and often obscure, a later era characterized by the appearance of more severe but remittent clinical phenomena, and a third and final stage in which severe symptoms are continuous. As such a classification would appear to facilitate description, we may then divide pellagra into

(1) An early form of the malady in which there is progressive physiologic deterioration of the entire body accompanied by dyspeptic and nervous symptoms:

(2) An intermediate period during which the clinical phenomena are more severe, there being recurring attacks characterized by one or more of the classical manifestations recognized by all writers, but between which the patient enjoys periods of fairly good health, and

(3) A final stage in which one or more of the severer clinical phenomena persists throughout.

First stage (pellagrous neurasthenia).—It is an interesting fact, though scarcely to be regarded as remarkable, that all practicall pellagrologists, even from the earliest periods, have recognized that the symptomatology of pellagra is not limited to those obvious and very pronounced phenomena which ordinarily characterize the fully developed disease.

Casal, Zanetti, and particularly Gherardini and Strambio, all insisted that the eruption is frequently preceded by a period of days or even weeks, during which the patient complains of vertigo, mental and physical depression, loss of appetite, burning in the mouth and stomach, and a feeling of heaviness, often accompanied by pains of an indefinite character in the abdomen, back and limbs. Similar observations were made at a later time by Fanzago, Nardi, Brierre de Boismont, Theodori, Roussel, and Lussana and Frua,—the two last named writers regarding these earlier manifestations as constituting an essential and integral part of the clinical picture of this malady; this is called by them the stage of hypochondriasis (mal del padrone). They particularly direct attention to the importance of pyrosis fol-

lowing the ingestion of maize products as a symptom which ushers in the pellagrous attack. It is noteworthy that these writers assert that care and attention at this period as a rule quickly causes the patient to improve, the further stages of the pellagrous attack being thus warded off. Babes and Sion likewise recognized these earlier symptoms as constituting the beginning of the pellagrous attack.

At this point it appears advisable to discuss briefly the nature of these mild clinical phenomena that in some degree always precede the typical pellagrous onset. The advocates of the view that maize produces pellagra have been, it appears to the author, quite generally misled as to the true nature of the acute attacks,—appearing always to have assumed that they are a consequence of an intoxication which has occurred immediately before, and the earlier manifestations are regarded as constituting a sort of period of incubation, however illógical this view might appear to be under the circumstances. As to just how far the recurring pellagrous attacks are influenced by the eating of maize immediately before their outbreak it is impossible to determine at the present time, but the author is inclined to think that such influences play an entirely subordinate role. Much more probable is it that the acute symptoms result from a combination of the altered metabolism brought about by the lesions and the accumulated evil effects of many debilitating conditions under which pellagrins generally live. During the winter the agricultural classes in the main cease active, outdoor exercise, and spend their time in ill-ventilated houses, and live on a very restricted dietary,—there being months during which they consume little or no vegetables, and subsist largely on indigestible salt pork and maize bread. When the farmer, enfeebled by such influences, begins his spring work in the fields his resisting power is decreased by the sudden tax on his strength, and his predisposition to the typical manifestations of pellagra are greatly enhanced by the action of the sun's rays. To the above is added in some countries, as in Roumania, long and severe fasts during the lenten season, and which Babes states is frequently followed by the appearance of this affection. It should also be remarked, as would naturally be inferred, that persons weakened by previous disease are far more liable to pellagra than others, and it has often been noticed that alcoholics are peculiarly prone to the malady. Under the conditions referred to then we find individuals, particularly those who are weakened, developing pellagra in the late winter, or, with even greater frequency at the period when they begin to expose themselves to the sun and commence the strenuous labors of the spring. At such times pellagrous individuals quickly show the effects of the strain, and begin to exhibit the symptoms which we shall presently consider many weeks preceding the frank outbreak of the malady. While the fact has been partially recognized, no one seems to have insisted upon the frequency of the occurrence of these earlier manifestations *without* the subsequent development of the classical pellagrous symptoms, but that this is extremely common there can be no question. It is furthermore frequently true that the malady develops no further. Indeed it may be said that a great majority of pellagrins never show the graver mani-

festations, and live throughout life suffering occasionally from recurrences of the mild attacks, but quickly recovering on the bodily resistance being improved. According to the author's view then only those persons become pellagrous, in the ordinary acceptation of the term, whose tissues have been profoundly altered by the poisons that produce the malady,—this being particularly apt to occur in those with weak digestions, in alcoholics, and in those who have been subjected to mental strain or great sorrows, and who have been the victims of chronic diseases of any kind; the malady also often follows pregnancy, lactation, and develops after operations or injuries.

We will now consider the nature of these earlier manifestations:

After many years of observation it appears to the author that *constipation* is in all probability the earliest symptom of pellagra. With the rarest exceptions patients will admit on close inquiry that they were well up to the time when sluggishness of the bowels developed,—this having generally occurred many years before they sought medical advice. Following this there is usually a long period during which there is a *gradual deterioration in health,* with a corresponding loss in weight in the great majority of instances.

Coming on almost simultaneously changes in the tongue take place which consist in the beginning only of a *permanent light coat.* There may also in addition develop *hypertrophy of the papillae,* though this alteration is usually not marked and affects only a comparatively small number of these bodies. On the tongue being protruded it is likewise the case that in many of these individuals it *will not describe the normal parabolic curve,* but on the other hand is *protruded horizontally* and not infrequently has a *trough-like appearance;* this peculiarity is thought by Gemma (4), who has treated this subject in a masterly manner, to be the result of inequalities in the strength of the component muscles of the organ. Attention was first directed to the changes in the mucous surfaces just described by those eminent Italian pellagrologists Lussana and Frua, who declared that they are frequent in the peasantry of Venice and Lombardy, though occurring in individuals who had never suffered from pellagra; they were not inclined to regard them as being primarily symptoms of this malady, but simply a condition resulting from disturbances of the alimentary tract the consequence of eating improper food. Similarly the author has frequently seen such alterations in persons not pellagrous in the ordinary sense of the word, but he has no hesitation whatever in asserting that they often constitute the earlier oral symptoms of the first stage of this affection.

Closely related to the lingual changes just mentioned are the alterations in the tongue that are quite commonly encountered in the offspring of pellagrins, representing in all probability a more advanced stage of the pathologic process upon which they both depend. Here we likewise find the tongue *habitually coated,* but where the underlying tissues are visible it is seen that they are *abnormally red.* Here also the *papillae undergo hypertrophic changes,* though the process is and by no means uniform over the whole surface. The fissures normally occurring on the top of the tongue are deepened,—this pro-

cess going on in many instances until the upper surface of the organ appears distinctly *lobulated;* in some instances there is likewise seen *papillary protrusions* around the edge of the tongue, giving it a fringed appearance; this condition should not be confused with that in which the dental impressions are left on the margins of the organ, for this is not uncommonly observed in these subjects. Inspection with a hand-lens will show that there is no actual destruction of the epithelium covering the papillae or general lingual surface. Gemma (4) has particularly called attention to the fact that in these patients the tongue is often *protruded in an oblique fashion,* and that careful measurements will show the *thickness* of the organ to *vary* somewhat on the two sides,—both conditions being due to an irregular action of the lingual muscles.

It should not be forgotten in this connection that these unfortunate descendants of pellagrins likewise show *evidences of degeneracy,* there being not uncommonly *under-development of the body, anomalies,* particularly of the face and head, and a *low order of intellect.* For a more complete consideration of this phase of the subject the reader is referred to the chapter on hereditary pellagra in children.

Simultaneously with the occurrence of the symptoms just described the patient *loses his former mental and bodily vigor,* and he has a tendency to the "blues," the attacks of which, in some instances, become more and more frequent until finally the unfortunate victim is in a state of *continuous melancholy.* Frequently he becomes *hypochondriacal* and spends the greater part of his time mentally recording and analyzing the various unpleasant symptoms which gradually increase in number and severity. *Pains of an indefinite character* are frequently complained of in the *head, back of the neck,* in the *abdomen,* and occasionally in the *limbs.* One of the most constant and disagreeable of the subjective sensations is *vertigo,* of which almost all pellagrins complain more or less. The patient is sometimes annoyed by a feeling of *"pins and needles"* in the hands and lower extremities, and in some instances it is possible to observe evidences of *impaired sensation to touch;* the power of perceiving *pain* and *heat* and *cold* do not appear to be interfered with to any extent as a rule, nor is the *muscle sense* altered. With a further advance of the process patients develop marked *digestive disturbances,* usually manifested by *pyrosis,* a feeling of *burning in the stomach, esophagus or mouth.* Quite generally there is *loss of appetite* and the patient complains of "biliousness," accompanied by marked physical depression. Disturbances of the *special senses* are occasionally observed, as, for example, patients complain that all food tasts unusually *salty,* of *ringing in the ears,* and *disturbances of vision.* Now and then *pains* are encountered in the *joints.* There is nearly always more or less *loss of weight.*

The foregoing symptoms are those which are usually encountered in the earlier stages of pellagra, though it is rarely or never the case that they are all exhibited by the same individual. From the time that the patient develops the disease, however, he, in the vast ma-

jority of instances, suffers at all times from one or more of these manifestations. In some instances, particularly where the patient is naturally strong, a change of climate, or a great improvement in hygienic surroundings is followed by an almost entire cessation of these unpleasant phenomena, but they recur again within a short time should his general health suffer from any cause. It is almost invariably true that exacerbations occur in the early spring, to be followed in the late summer by decided improvement, and a return almost to the normal in the earlier months of the winter in many instances; however, along about Christmas, or a little later, the patient's health becomes again impaired, and the following spring finds him as a rule with a recurrence of all of his earlier unpleasant symptoms, with not uncomonly the addition of others. At such times it not infrequently happens that the patient's *mouth will get a little sore,* and he will have *flurries of diarrhoea,* immediately followed, however, by the customary *constipation.* Simultaneously an annoying *sense of heat in the backs of the hands and feet* is frequently complained of, which may be so severe as to cause great discomfort; *burning in the mouth, esophagus or stomach* is not uncommon, accompanied by *great loss of strength,* and an *increase in the mental depression* and in the *severity of all of the indefinite nervous disturbances* from which the patient has previously suffered. Even in this early stage women very frequently complain of a *leucorrhoea,* which is, at least partially, due to a *vaginitis;* as to whether under such circumstances there is likewise an *endometritis* is not as yet known, though extremely probable.

At this stage likewise *objective skin symptoms* may be frequently observed. They consist in a *wrinkling,* particularly on the *backs of the hands,* and as a consequence the skin in this situation presents to a greater or less extent the characteristic appearances which come on with senility. Moreover the skin often appears *yellow* just preceding an outbreak, and in rare cases it is said that the entire body may assume a *darkly pigmented* appearance, which is permanent. We also often observe, either alone or in combination with the foregoing, a *pecuriar dryness* of the skin, with the formation of *minute scales.* This scaliness is most common and severe on the exposed portions of the skin, but may occur on any part of the body. The scales may be pigmented. Gemma calls attention to the occasional occurrence of *maculae* on the skin; these spots may not present a deep color, being often of a yellowish tint. They are most common on the face, and may persist for years. On microscopic examination we find frequently in the upper layers of the derma a flattening of the papillary bodies, disappearance of the collagenous tissue, and the presence of great masses of swollen collacin, which usually differ from the similar appearances particularly observed in old persons who have been much exposed to severe weather conditions in that the alterations are more severe, and frequently extend outward to the epithelial border.

The author agrees with Lussana and Frua that if patients at this time be put to bed and looked after properly they usually return to a fairly good state of health in a short time, and he further thinks that subsequent acute attacks of the disease may in many instances be

warded off by continued care, though if the victim lives long enough a time is doubtless always reached when his resistance can be no longer sufficiently maintained, and he then develops the phenomena that characterize the classical outbreaks of the malady.

While it is true that no one of the manifestations referred to can be regarded as pathognomonic, the author is firmly of the opinion that by the time the patient seeks medical advice he probably always suffers from a combination of symptoms which is extremely characteristic; there is almost always a history of previous constipation and indigestion, loss of strength, mental depression, decrease in weight and vertigo, which, along with the frequent occurrence of sore mouth, burnings in the hands, feet, stomach, esophagus or tongue, loss of appetite, and general malaise, together constitute, particularly when they occur in the spring, a combination of pellagrous phenomena that can hardly be mistaken.

In concluding this phase of the subject the author would reiterate his conviction that the symptoms recorded in the preceding pages, together or in part, correspond to and are the result of the pathological alterations that occur during the earlier periods of the pellagrous process, and that their recognition is of the first importance from the standpoint of an early treatment. His conviction is equally strong that these phenomena are not merely the outer expression of a temporary and quickly passing intoxication, but that they are the external manifestations of morbid alterations that are either wholly or in part permanent, and that an individual who has once exhibited them should ever afterwards be looked upon as potentially a pellagrin—however completely he may appear to have recovered. At least in one instance the author knows of a case where a lady suffered from just such symptoms in the spring for a period of twenty years, and then suddenly developed a typical pellagrous attack, followed by death. He does not believe that it is necessary that these patients should continue to eat maize products in order for the clinical manifestations to recur, though doubtless the frequency of the outbreaks and the severity of the symptoms will largely depend upon the amount of this grain consumed. The pathological changes once inaugurated,—bearing a close relationship to those of senility—probably go on increasing with the lapse of years, even under the best conditions, and it is only necessary for the patient's resistance to be suddenly lowered for the old attacks to be repeated or even a frank outburst of classical pellagra to occur.

To this state of the disease the author has for convenience ventured to give the name *pellagrous neurasthenia.*

It must never be forgotten that the first stage of the affection may at any time terminate in a more or less *complete loss of intellection.* Likewise it may happen—and such cases are in the author's experience the most malignant—that with scarcely any warning the foregoing symptoms may culminate in the sudden development of pronounced mental symptoms.

Sooner or later many of these patients pass into the second stage of the disease, which will now be described.

THE SECOND STAGE (classical pellagra).—The second stage of pellagra, as described by the author, comprises all of those classic manifestations which we have been in the past generally taught to regard as together constituting the symptoms that go to make up a typical attack of this malady. Such attacks usually take place in the late winter or early spring, though they may occur in the summer or autumn, and even under exceptional circumstances in early winter. Where the onset is typical, symptoms usually come on without any discoverable predisposing causes, though not uncommonly the patients acknowledge having suffered from debilitating influences shortly preceding the outbreak; particularly has the author been struck by the frequency with which women give a history of a preceding great sorrow, or excessive and unusual worries, and they likewise not uncommonly ascribe their decline in health to childbirth, lactation or the menopause; there can also be no doubt that the attacks are determined frequently by exposure to the sun, or occasionally by injuries of the skin produced by heat or mechanical agencies.

This stage is characterized by the development of one or more of the classic symptoms of pellagra,—the skin changes and the alterations in the mucous membrane being far commoner than pronounced mental alienation. These manifestations come on in all instances following an indefinite period of greater or less decline in the general health, during which the patient suffers from the symptoms which have been described as characterizing the first stage of the disease. Not only has the victim from time to time suffered from more or less distinct attacks of this character, but in a great majority of instances the frank outbreak of the second stage of the malady is preceded by a period of pronounced ill health, lasting from two or three to six or eight weeks, and during which the patient is particularly apt to exhibit marked disturbances of the digestion, great bodily weakness, and mental depression.

In over 50 per cent. of cases Tambroni has noted asymmetries of the face.

We will now consider seriatim the symptoms of a typical pellagrous attack:

SKIN SYMPTOMS.—As a rule the skin of pellagrins is dry, and perspiration is reduced; in some cases, however, this is reversed and sweating is excessive, as has been observed by Lombroso.

Antonini (5) has observed that there is an increase in the secretion of the sebaceous glands of the nose in some pellagrins

It should be also noted that many different kinds of discolorations occur in the skins of pellagrins; not only do we have the appearance produced by anaemia, but, as noted by Gemma (1), there may be a curious yellowish color of the skin in addition, which is but little influenced by the state of the blood, and may be in some instances very chronic; we likewise find about the face not uncommonly large irregularly shaped areas of yellowish or brownish discoloration, and in rare cases there are scattered over the body deeply pigmented maculae which are at times almost jet black; on those parts of the body commonly the site of the skin lesions pigmentation is also not un-

common, and may become so pronounced as to produce great disfigurement; likewise we have a condition probably associated with disease of the adrenals where the entire body is bronzed. The *skin of the entire body often becomes darker before* and *during* an actute attack, but more often it is mainly observed on the hands, face, neck and chest. The skin, in old pellagrins, may present an *earthy* appearance.

It should never be forgotten that pellagrins as a rule *show a premature wrinkling,* which is associated with atrophy of the skin.

Following the common usage among dermatologists, and likewise for the sake of convenience, Majocchi (3) some years ago urged the propriety of designating the skin lesions of this disease by the term *pellagraderms,* and as his position seems to be well taken it has been thought advisable to follow his suggestion in this matter.

He classifies them as follows:

- Pellagraderms
  - Erythematous
    - Common
    - Erysipelatous
    - Erythemato-papular
    - Erythemato-macular
  - Haemorrhagic
  - Vesicular or pemphigoid
  - Follicular
    - Seborrhoeaic
    - Warty (hyperkeratosis)
    - Acneous

In probably a majority of instances the second stage of pellagra first manifests itself objectively by the occurrence of *skin lesions,* though perhaps almost as frequently the *mucous membranes* are first affected; in a considerable proportion of cases no skin changes show themselves.

The percentage of cases in which the characteristic dermal lesions make their appearance, as well as the relative frequency with which such changes appear in various parts of the body in ordinary pellagra, is very well shown by the statistics of Weiss, collected by him for the Austrian government. Among 4,836 pellagrins 2,972 exhibited pellagraderms, and of the latter 2,179 were specifically catalogued as having had a typical erythema; of these 77 per cent showed the lesions on the backs of the hands, 13 per cent. on the hands and neck, 7.5 per cent. on the neck alone, and 2.4 per cent. on other parts of the body. Such figures cannot, however, be regarded as universally representative, since these lesions are unquestionably greatly influenced by external agencies,—the sun particularly playing an important role

in their development, as was first demonstrated experimentally by Gherardini, and later by Strambio (4), and others. The effect of solar action is shown in a marked manner in this country by the almost universal occurrence of skin lesions on the backs of the hands of the pellagrins of our agricultural classes, while such manifestations are not by any means so common in those who spend their lives largely within doors. Of similar import is the assertion of Vales that in Mexico patients show pellagraderms on the backs of their feet more commonly than in Europe, which fact this author thinks is attributable to the almost universal habit among the poorer classes of going barefoot. In this connection the case related to Neusser (1) by Sapunzachi is very interesting; the patient was accustomed to walk in the open with his hands crossed behind his back, and the pellagraderm instead of developing in the usual situation appeared on the palmar surface of the hand which was commonly exposed to the sun's rays. However, it is important to recognize that pellagraderms may and frequently do occur quite independently of solar action; occasionally they may result from undue exposure to heat, and may take their origin from local injuries, and, as has been observed by Pearson, are very apt to occur in those situations where the skin is irritated by tight garments.

The *characteristic cutaneous lesions of pellagra begin,* as was first noted by Raymond, *with considerable suddenness,* developing in the course of twenty-four hours, after a prodromal period of greater or less length. Ordinarily the *pellagraderms begin simultaneously on the two corresponding sides of the body,* and the lesion gradually extends from the point at which it first appears.

While quite red in the very beginning typical pellagraderms quickly take on more or less of a *livid appearance,* which increases in intensity as the lesion grows older. In the earlier stages there is a pronounced dilitation of the blood vessels, and the affected parts may be therefore *discolored by firm pressure,*—to be instantly followed by a return of the reddish hue on the pressure being removed; at a later time hemorrhages frequently occur into the tissues, and, of course, under such circumstances the color of the parts can no longer be influenced by mechanical means.

While they were first described by Gemma (1), Merk (2) has recently rediscovered the fact that in pellagra a *preliminary rash* occurs in a certain number of cases, presenting itself as *discrete maculae* that last from a few days to a week or so; these spots are true maculae in the dermatological sense, of a red color, not raised above the surface, and cannot be considered sufficiently characteristic to possess diagnostic importance. They are frequently symmetrical.

Gemma (8) has also described an early *pellagrous papular erythema,* characterized by small red papules in those situations where the more common lesions occur.

As pointed out by Gemma (1) the redness of the atypical pellagraderms may subside after two or three or more days, leaving little or no after effects; whether such lesions are really pellagrous, or whether they are to be generally regarded as due to some other cause,

such as sunburn, is difficult to determine, but the author fully agrees with this writer in the statement that the amount of solar action necessary to bring out such disturbances is much less in pellagrins than in normal people.

As a rule the characteristic pellagraderms begin on the *backs of the hands near the bases of the fingers.* The lesion gradually extends until in most cases it *covers the entire backs of the hands* and the posterior surface of the two *proximal phalanges;* rarely the process extends to the *tips of the fingers.* In two instances the writer has seen the lesion invade the *palms of the hands.* The erythema may remain confined to the backs of the hands, or may gradually extend upward to the *wrists* and *lower part of the forearms,* and occasionally ascends the outer aspect of the latter to a considerable distance,—in some cases gradually creeping up until it reaches the *arms,* and exceptionably extending up over the *shoulders.* The tip of the elbow often shows the lesion, even where the surrounding skin is normal.

Similar changes are observed on the *backs of the feet,* though they are by no means so common as in the localities already mentioned. This lesion usually either follows or accompanies similar alterations on the hands, but in rare cases it occurs on the backs of the feet alone, and remains confined to this area and the lower portion of the legs.

Quite often pellagraderms are observed on the *face,* beginning usually on the *bridge of the nose,* and over the *cheek bones,* thence extending in very rare instances to the *chin* and *lips;* when pronounced, such lesions are sometimes called the "pellagra-mask."

Not infrequently the lesion is observed around the *neck,* with an extension down the *sternum,* giving rise to the so-called "Casal's necktie."

In rarer instances other parts of the body may be affected, the change being observed on the arms, on the skin covering the *popliteal space,* on the *scrotum,* around the *anus,* and in the *perineal region.*

Deiaco, Fiocco,(1), Bravetta (2), and E. Verga have recently described and figured a number of interesting cases showing atypical locations of pellagraderms.

In some instances the *lesions cover the entire body,* two examples of which have recently occurred in the author's practice. Some of the best writers have denied the possibility of such universal skin lesions, but, in addition to the cases just referred to, Sandwith (2) speaks of all parts of the body being affected in severe cases under some circumstances. Recently a case of this character has been reported by Miller, and the author saw another with his friend, Dr. McCurdy, of Shellman, Ga.

Atypical lesions are apt to occur in very severe cases, a point particularly insisted upon by Fiocco.

For the first few days the reddish-livid lesion in typical pellagraderms is fairly smooth, there being up to this period but little change in the epiderm; after this, however, hyperkeratosis manifests itself and continues throughout the course of the eruption,—beginning first in the central portion of the lesion and gradually extending

outward. This is accompanied by *scaling,* which *likewise begins where the lesion first manifested itself, and follows it outward in every direction. The scales are small, usually dry, of a grayish color, and are angular and much resemble bran.* In many cases the typical lesions exhibit an abortive tendency: under such circumstances the skin often becomes slightly red, to be followed in three or four days by scaling, and a return to the normal,—the entire process not taking more than six or eight days. *This is in some instances frequently repeated throughout the hot months.* The desquamation may be accompanied by *no visible redness,* and in rare cases *continues for weeks,* or even *months.*

As a consequence of an increase in blood and exudation of serum into the derma, the skin swells, and the elevations and depressions, normally present on its surface, become accentuated and impart to the diseased area a *wrinkled appearance.* Under ordinary conditions the process begins to show some *amelioration in the course of ten or twelve days,* after which there is a gradual improvement and a return in the course of *six or eight weeks* to a more or less normal condition. In some cases, however, the *wrinkling* already referred to remains marked for a considerable period of time, and not infrequently persists permanently; under such circumstances the contrast between the aged appearance of the backs of the hands and the smooth youthful aspect of the skin of the face is most striking.

In young individuals after two or three months no visible effects are left on the skin in some instances, but in the great majority of cases the parts never return entirely to the normal. Particularly after two or three repetitions the skin becomes *thickened, rough, wrinkled,* and *frequently pigmented.* In old pellagrins a very characteristic skin lesion is frequently seen, particularly on the backs of the hands, the skin becoming *dry, smooth, glossy,* with a *parchment-like consistency,* and *great loss of elasticity;* under such circumstances the *derma is evidently greatly thinned,* and where it is replaced largely by serum the skin requires a transparent appearance, which is most curious and highly distinctive. While this alteration usually follows repeated attacks of the erythematous pellagraderm, the author has seen it in many instances where there was no history of a pronounced acute skin lesion. The change is evidently closely connected with the alterations first described by Neumann as senile change, and later associated by Unna (2) with *exposure to the weather.*

The typical course and termination of the ordinary pellagraderms is oftentimes complicated by the formation of *blebs* and *pustules,* and for which Majocchi has suggested the name of *pemphigoid pellagraderm.* These lesions are most common on the backs of the hands, but are occasionally encountered on the feet, and even other parts of the body; when rupture occurs ulcers, which may later scab over, are not uncommon. The same writer speaks of an *erysipelatoid* variety of the lesion, this being characterized by a greater degree of redness than usual, but which does not extend in the same manner nor to such an extent as ordinary erysipelas.

Likewise in severe forms of the disease *deep cracks* or *sulci* may develop in the skin, either during the period of greatest activity of the inflammation or toward its termination.

In some cases Gemma (1) has seen the lesion take on the appearance of a *true eczema.*

Majocchi (2) has also recently called attention to a *seborrhoeic form* of the disease, and observes that it usually has its site on the nose, on the cheeks, or more rarely on the hands and breast. Similar lesions have been recently reported by Pearson, and have been noted by the author in one case. These alterations are most common in old cases, are very chronic, and are clinically manifested by small elevations from the size of a grain of wheat to that of a filbert scattered here and there over the diseased area, and containing an abundance of acid-smelling, sebaceous material. These lesions were first described by Gemma (1) as *miliary lichen.*

Still more recently Zilocchi (2) has observed *comedoes* developing on the skin of the face preceding an active outbreak of pellagra. The author has frequently encountered similar lesions, and has not uncommonly seen them complicating mild or protracted forms of *acne,* particularly affecting the forehead, the bridge of the nose, and the concavity between the lower lip and chin.

Closely related to the lesion just referred to are certain pellagraderms to which Strambio (4) first called attention. These lesions are likewise found in the chronic forms of the disease, and consist in the formation of *purplish papules,* usually on the chest and back, which sometimes, though rarely, go on to suppuration,—thus giving rise to small boils, but which are almost painless; they disappear usually in the course of a few days, to be followed by others in neighboring areas. These lesions are doubtless merely the result of a vitiated digestion, and are not to be regarded as in any way specific.

Gemma (8) first called attention to *pemphigus* caused by pellagra.

Strambio (4) has likewise called attention to the occasional occurrence in pellagrins of a *herpetic eruption* which appears on the hands, face and other parts of the body, and Gemma (1) has observed occasionally on the legs of women a *curious marbled appearance* which is produced by alternating areas of livid and normal skin.

Gemma (8) has described a pellagrous *papular erythema.*

Another interesting skin lesion, to which Strambio (4) first directed attention, consists in the formation of *localized purpuric spots* on the backs of the hands and sometimes in other situations. These areas are the result of hemorrhage, and follow perhaps in all instances trauma, though not uncommonly this is of so slight a nature that the patient's attention is not even directed to it at the time of its occurrence. The ease with which lesions of this kind may be produced is readily undersood on examining microscopically the greatly altered skin in the more chronic forms of pellagra, the derma being greatly thinned, and made up of large cavities, filled with serum, in which lie loosely bundles of more or less altered connective tissue and elacin, and almost bare blood vessels, the surrounding supporting structures of which have been almost entirely destroyed. Similar

lesions hace been observed by Majocchi (2) in the mucous membranes.

In addition to the not uncommon tendency to desquamation in pellagrins there is occasionally observed in such subjects, as first noted by Calderini (2), a singular condition as the result of which the surface presents much the same scaly appearance exhibited by the skins of fish. Also well-marked *ichthyosis* has been described by Gemma (8), and more recently noted by the author in pellagrins.

In this connection the author would express his entire agreement with Neusser (1), who states that pellagra may occur as an *essential dermatosis* unaccompanied by any of the other classical symptoms of the disease, though such patients invariably admit on close questioning having had some of the milder clinical phenomena to which attention has already been directed.

It is hardly necessary to say, after what has been written already on the subject of symptomatology, that the writer is moreover wholly in accord with those who believe in the very common occurrence of *pellagra sine pellagra.*

As first pointed out by Strambio, *the severity of the skin lesions bears no relationship to the intensity of the other clinical manifestations.*

It is of interest to note that *edema* of the face and ankles is now and then found in pellagra.

Changes in the finger nails appear to have been first observed by Gherardini, he having noted that they sometimes become deformed (p. 37). Lombroso (11) records that he saw four cases in which there was enlargement and deformity of the finger nails,—in two instances being alone on the left hand. Gemma (1) has described a pellagrous *onychogryphosis,*—there being a false form where the nails curve inward, and a true variety where they become hypertrophied and deformed. Tonnini has also observed changes in the finger nails in the tabetic form of pellagra. Still more recently Alpago-Novello (2) has asserted that demonstrable changes occur in the finger nails in 94 per cent. of cases, and Antonini (5) has stated that such changes are common. The latest paper on this subject is one by E. Verga, who found marked alterations in the nails of the hands in 4 per cent. and in those of the toes in 2 per cent. of all cases; less marked but obvious changes were found in 10 per cent. of the cases in the hands and 22 per cent. in the feet.

As would be indicated by the nature of the pathologic alteration in the skin the hair does not as a rule suffer greatly; in some cases, however, there is marked loss and *premature grayness* may develop, as pointed out by Gemma (1), and may be accompanied by *loss of the pigment* in the neighboring skin as this accurate observer noted; such changes may occur in the eye brows. The *hair* is often *thin,* and *dandruff* is not uncommon. In one instance the author saw an *overgrowth of hair* on the thighs and legs of a pellagrous woman.

It was noted by Gemma (3) that the *hair develops slowly* and *imperfectly* in hereditary pellagrins.

GASTROINTESTINAL TRACT.—Quite as frequent, and of more importance clinically than the skin changes, are the lesions that are commonly found associated with pellagra in the gastrointestinal tract. Some of the consequent manifestations are of the first diagnostic importance, while still others are of the greatest moment from the standpoint of treatment. For the sake of convenience the symptoms connected with the various parts of the alimentary tract will be separately considered.

Mouth and throat.—From the time of Casal changes in the *tongue* have played an important part in the symptomatology of pellagra, but it was reserved for the great Italian pellagrologist Gemma (4) to give an accurate account of the various and peculiar alterations that occur in the oral cavity, and to direct attention particularly to the resultant symptomatology.

As pointed out by the great observer just referred to, it is quite characteristic of pellagrous lesions that *they are almost wholly confined to the superficial layers of the mucous surfaces,* and it may be added that this is also a striking peculiarity of the skin change, and that the toxine that produces the disease has unquestionably an affinity for not only the epithelial structures, ordinarily so considered, but likewise for the cells in the central nervous system that take their origin from the epiderm. The author just mentioned likewise points out that generally speaking the *mucous surface of the mouth and throat is not uniformly affected,* but that there are areas of epithelial change, with more or less hyperaemia beneath, surrounded by zones comparatively healthy. Likewise there is a general tendency to *serous effusion into and exfoliation of the epithelial coating,* followed—when such lesions occur—by an *extension of the pathologic change into the deeper tissues,* —it being rarely the case that catarrhal alterations are secondary to the envolvement of the deeper structures. It is further pointed out that these lesions, while often occurring simultaneously with neuralgias, and intestinal and skin alterations, have no necessary connection with them, as in the first instance there is no *observable tendency for the alterations to occur in the area of distribution of any particular nerve,* nor is *it usual in the latter two conditions for the inflammatory process to extend into the mouth by continuity of surface;* it is therefore clear that all of these lesions are due to some general cause, with a tendency to rhythmical recurrences.

Catarrhal changes of the tongue, as pointed out by Gemma, may be considered as the point of departure from the normal in the development of the mouth-changes in pellagra. This alteration presents itself as *rounded, whitish, smooth, polished areas* about a millimetre in diameter, not elevated above the general surface and found most commonly at the *base* and at the *tip* of the tongue. In some cases, particularly in children, the spots are larger, being one or two centimetres in diameter.

Gemma is particularly insistent that such changes should not be regarded as evidence of a beginning gastritis, as under such circum-

stances purgatives are likely to be ordered, with the production not infrequently of a fatal diarrhoea.

Following the alteration just described the epithelial cells shed off, and, as they are not at once replaced, there results a *solution of continuity of surface,* and the *formation of shallow ulcers;* while these areas are always at first superficial they often penetrate somewhat into the underlying structures,—the deeper the process the more pronounced the swelling, redness, soreness and other evidences of inflammation. This process is *very acute* in its beginning, it requiring only a day as a rule for complete exfoliation to occur, but the *subsequent course is generally quite chronic* and lasts well into convalescence.

Exfoliation of the epithelial coating of the punctiform papillae is a very common and characteristic alteration, and is distinguished by a great number of *minute points of a reddish color* which show strikingly on a field of white coating; these spots are *circular, oval,* and the *largest* is not more than a *millimetre in diameter,* the mean being about half this size. This alteration *occurs toward the end of the tongue,* and is never seen back of its middle. Not uncommonly the *lesions are localized along the borders and apex of the tongue.* It is evident that such changes are consecutive to softening of the epithelium covering the papillae,—its exfoliation being accelerated by the constant movements of the organ. This alteration has an important bearing on the symptomatology of pellagra, because it is often the first symptom of epithelial change in the intestinal tract, and, especially in children, may throw early light on the true nature of the trouble. They are distinguished from similar areas on the general surface of the tongue by the fact that they are *very red, quite uniform in size,* and *somewhat elevated* above the surrounding surfaces.

Diffuse epithelial exfoliation is also sometimes observed under such circumstances, the surface of the tongue becoming *redder* and *smoother,* the areas of change being *irregular* in *form* and not uncommonly having a *ribbon-like appearance;* it is somewhat more frequent on the *anterior surface* and *borders* of the organ. As the lesion deepens its surface becomes still redder and appears swollen. Particularly in *old cases,* where atrophic changes have occurred in the tongue, these lesions often exhibit a *bluish appearance,* which results from the presence of numerous veins just beneath the surface.

Minute vesicles may complicate the early changes in the epithelial coating, and may present themselves at the period when only nervous and muscular symptoms are beginning. They are ordinarily not *discernible with the naked eye,* but may be perfectly made out with a hand lens; they occur on the tops of the papillae, and are so numerous that they touch each other; they are filled with a very transparent liquid. Occasionally one of the vesicles will be of greater size, and project above the general surface.

Acute glossitis and stomatitis is a frequent occurrence in the earlier stages of a pellagrous attack, and comes on following the changes in the epithelium, to which attention has already been directed. In this case the tongue is often *edematous* and *covered by vesicles,* and on palpation *similar lesions may be found in the lips and cheeks and gums.* The tongue acquires an *increased temperature,* and *becomes thickened,* and is at first heavily *coated; desquamation* then occurs and the organ becomes *irritated, swollen,* and of a *vivid red,* which in some instances is shiny. In very mild cases actual ulceration does not occur, but generally these alterations are present to a greater or less extent; frequently these excoriations take their origin from the bursting of the blisters just referred to, while in other cases they develop here and there from destruction of the epithelial coating, and form more or less elongated furrow-like ulcers. Not infrequently the *process penetrates into the underlying submucosa* and gives rise to *suppurating ulcers.*

The *functional disturbances* that follow these alterations are quite pronounced, there being *salivation* and *difficulty in mastication.*

The course of the inflammation is quite acute where excoriations do not develop, lasting only a few days. On the other hand, where ulcers form, the process is much more chronic.

Papillary ptosis is the name employed by Gemma to designate a condition of destruction of the conical and filliform papillae of the tongue, which occurs only in chronic forms of pellagra. As a consequence of the change the *surface of the tongue presents a smooth and polished appearance,* and seems to be *composed of homogeneous tissue.* The alteration may occupy a large part of the tongue surface, though occasionally it is encountered as small islets. In some instances it is accompanied by hypertrophy of the other papillae, especially those of the fungiform type. Sometimes, according to Lussana and Frua, *scabs form* in cases where villi are in the process of being replaced. Where improvement occurs the swelling becomes less and the villi slowly reform over the injured surface. One should be careful to distinguish between this form of the alteration and a simple swelling of the tongue, which may closely simulate it.

The alteration is particularly common in *hereditary* and *confirmed pellagra* where the patient has a greatly lowered vitality.

Papillary hypertrophy is likewise a change not uncommonly observed in *old pellagrins,* and occurs with regularity in the more marked *hereditary forms* of the disease, being in some cases primary and in others secondary to earlier changes in the organ, and representing an attempt on the part of nature to restore the affected parts to a normal condition. Under such circumstances when the finger is passed over the tongue's surface the effect produced is likened by Lussana to that observed when we displace the ends of the bristles of a whist-broom. Gemma says that when this condition occurs during the course of acquired pellagra it is always accompanied by intestinal symptoms.

The *conoinversiform* or *capitate papillae* are sometimes *considerably enlarged,* acquiring the size of a grain of wheat in some cases.

Hypertrophy of the fungiform papillae likewise merits some attention, but is not common except in hereditary pellagra. These structures then are enlarged to the size of a grain of millet, and are raised above the surrounding surface.

Fissures of the tongue, first mentioned by Soler (p. 10), has been noted by nearly all of the writers on pellagra. According to Lussana these sulci run in various directions, but are transverse in the main. Gemma admits that furrows are normally present on the tongue, and deepen with age,—the organ wrinkling much in the same way that the skin does when subjected throughout many years to a constant repetition of similar movements. Particularly pronounced is the central sulcus, which divides the two halves of the organ; likewise there are two parallel but superficial depressions commonly present, and also one or two transverse fissures which arise on either side of the median line. The mechanism of the production of these fissures is not entirely clear, but they are supposed by Lussana to be the *consequence of irregular muscular contractions of the tongue* which is assumed to occur in pellagra, and which result in the gradual deepening of minute fissures that are ordinarily hardly observable; this supposition, of course, rests on the assumption that in the chronic forms of this disease *weakness* or *semi-paralytic conditions develop* in some of the tongue muscles. Gemma likewise urges as a causative factor *frequent swelling of the tongue,* there being under such circumstances a tendency to accentuate the lines which are normally present; where there is permanent enlargement the upper surface of the organ is crowded and pushed in toward the center, and as a consequence the furrows are much deepened. In some instances the explanations last given would not seem to be adequate to explain the occurrence of these furrows, since it is not uncommon for them to be observed in young hereditary pellagrins. These fissures *rarely disappear,* even when the patient gets well; on the other hand they commonly produce no trouble, and only have interest for the diagnostician.

During the acute stages of the process the tongue is *tremulous,* and retains at its edges the impress of the teeth.

Lividity of the mouth and pharynx is a peculiar condition first clearly described by Gemma, and which is to be distinguished from the acute inflammatory alterations previously considered. This process when present is *exceedingly characteristic* and *possesses a great diagnostic significance,*—indicating a chronic pellagra.

This lesion consists in the presence of a *peculiar livid color in the mucous membrane of the lips extending down to the gums, outward to the inside of the cheeks, backward beneath the tongue,* and *finally to the palate.* Where the lividity is marked on the roof of the mouth it presents a very striking and peculiar appearance, the process extending backward over the hard palate and ending abruptly in a sharp

line of demarcation at the point where the soft palate begins; the red border extends outward and downward on either side in front of the anterior pillar of the fauces. Similar alterations are frequently likewise encountered on the *vault of the pharynx,* as well as on its *lateral aspects;* the lesion is particularly marked near the median line and is also commonly found on the lower portions of the *pillars of the fauces.*

Associated with this lividity are *numerous tortuous* and *dilated veins* along its borders, along with which oftentimes a yellow line of fatty degeneration may be observed. With a hand lens we may also find here and there areas of *epithelial exfoliation scattered over these zones of lividity,* but the condition is not so marked as on the tongue. The mucosa surrounding the livid areas is not infrequently abnormally pale. Within the livid areas under the tongue, *spots of a wine red color two or three millimetres in diamater* are commonly encountered, and are undoubtedly *ecchymoses.*

It should be distinctly understood that these areas of lividity *represent rather a state of dilitation of the veins* than a true inflammatory process, though in those instances where the epithelium is destroyed changes of an inflammatory kind are naturally present; in some cases infections occur with *necroses of the superficial tissues,* the development of *mucous patches,* and *ulcerative* conditions.

It is interesting to observe that Gemma connects these peculiar livid areas with a *retardation in the circulation.* He points out that they are most pronounced on the hard palate and on the gums, in both of which regions he assumes that the close proximity of the unyielding osseous tissues conduce to venous stasis; likewise their occurrence on the lips he thinks is associated with the *loops that the blood vessels make at such points.* Such explanations, however, are not entirely satisfactory when it is remembered that the buccal mucous membrane is similarly affected.

These lesions are in no way associated with acute pellagra, but only come on after the disease has existed for a considerable period of time. Gemma says just as the *copper color in syphilis, the purple tint in scrofula, so are the livid spots in pellagra characteristic.* A careful histologic study of these lesions would be of extreme interest.

This lividity, when once developed, *remains throughout life,* becoming however more marked in the spring. It is frequent in *hereditary pellagrins.*

In one instance the author saw a remarkable *reddening of the mucosa* of the soft palate associated with the ordinary lesions of the mouth. (See frontispiece).

Thrush (*mughetto*) is a condition of the tongue and gums occasionally encountered in *chronic pellagra,* though it is more than doubtful as to whether it has any direct association with this disease. Lussana has observed it in a number of children, *the offspring of pellagrins.*

Majocchi (2) has observed areas of *haemorrhage* in the mucous membranes in this disease.

When acute outbreaks of the external symptoms of pellagra occur we first note that the tongue *becomes deeply coated,* the change being quite general, though more pronounced in certain areas. In some instances the organ is *edematous* and *covered with vesicles.* After some days *rounded* or *oblong areas appear on the ends and sides of the tongue which are produced by an exfoliation of the epithelial coat,* including the covering of the papillae, quickly followed by the formation of more or less pronounced *sulci* in case the inflammatory process be of a severe character. In addition there may occur one or more of the acute changes which have just been described.

Similar changes quickly follow in other parts of the mouth.

When *ulcers* form the *process is more prolonged,* and where recovery occurs the local condition gradually improves along with the general convalescence. The restoration to the normal does not occur in a regular fashion, there being areas which improve much more rapidly than others.

These phenomena recur again and again with each succeeding attack, and gradually the *mucosa acquires a hard, indurated appearance* which is extremely characteristic.

Similar acute alterations may occur in the mucosa of the pharynx, producing redness and in some instances actual ulceration. In the earlier stages of the process there may be frequently observed on the pillars of the fauces small areas where the *epithelium has accumulated* to such an extent that it forms *masses visible to the naked eye;* they usually have a diameter of from one to one and a half centimetres, and are characterized by a whitish, opaline, dirty appearance.

Gemma has called attention to a condition not uncommon in the pharynx of pellagrins, to which he has given the name of *pseudo-pellagrous angina.*

This is nothing more than an ordinary pharyngitis developing in a pellagrous individual, and is not regarded by this observer as being, strictly speaking, a pellagrous phenomenon. As this trouble however occurs at times in considerable epidemics and is almost wholly confined to pellagrous families, he thinks it merits a description along with the other clinical characteristics of this malady.

The affection usually develops in cold weather, and is *not accompanied by marked catarrhal change or by ulcerative or diphtheritic processes;* the inflammatory alteration is not of a pronounced character and as a consequence the surface does not become soft and boggy as in scarlet fever. Rarely it is followed by suppuration. It only exceptionally extends to the tonsils, or to the air passages, and remains therefore circumscribed and limited to a comparatively small area.

It is of interest to observe that this inflammation *only occurs in those who present the lividity of the mucous surface,* to which attention has been directed, and without which it would be impossible to consider that the affection had any relationship to pellagra.

During the course of the trouble the patient complains of an uneasy sensation in the back of his throat and of a peculiar dryness and difficulty in swallowing; the amount of disturbance is usually

out of proportion to the severity of the lesion, the patient complaining bitterly even when the degree of catarrhal change is slight.

Ordinarily the trouble terminates within a week, but may be prolonged to a considerably longer period.

Gemma is inclined to consider this condition as being largely the consequence of a very high degree of excitability on the part of the nerves of the mucosa, which in turn is the result of a lowered state of vitality. It is unaccompanied by fever.

Acute pellagrous angina.—This is a condition first described by Gemma, and is an inflammatory condition of the throat which this writer regards as being *directly the consequence of the pellagrous poison.* This affection *develops during the course of an acute attack of pellagra,* whether hereditary or acquired, and may complicate the mild forms of the disease without fever, or occur during the course of the severer types of the malady; it is seen sometimes in typhoid pellagra. Usually the affection occurs in the autumn and generally comes on during an acute exacerbation of other pellagrous symptoms,—an occurrence not uncommon at this period of the year.

The symptoms do not differ from those of the pseudo-angial form already described, though frequent exacerbations occur during its progress; it is also preceded by inflammatory conditions of the mouth, of which *it appears to be simply an extension by continuity of surface,* though it is of somewhat greater severity than are the lesions of the tongue. Thus in the pseudo-anginal forms there may be a simple punctiform exfoliation of the epithelium, while in the true pellagrous variety of the disease the catarrhal changes occur in connection with diffuse inflammatory alteration of the neighboring mucous surface, and with papillary ptosis. The condition ordinarily lasts from a week to fifteen days, and is quite amenable to treatment.

Characteristics exhibited by the oral cavity and pharynx in chronic pellagra.—Just as preceding acute inflammations of the skin leave their traces, so are similar changes in the tongue, when frequently repeated, finally followed by permanent effects, the degree of intensity of which depends of course on the severity and duration of these inflammatory attacks.

The tongues of those who have experienced repeated pellagrous attacks after a time develop a very peculiar and characteristic appearance; it is *long, thin,* and *unsymmetrical,* and is *lobulated* to a greater or less extent by the *formation of deep fissures.* In some instances the organ appears *curled,* and can only be *partially and imperfectly protruded,* or it may be that this *cannot be accomplished at all.* After many severe attacks it may appear, according to Gemma, like a *strip of cloth,* with scarcely greater thickness. In many instances *when protruded the sides of the organ curve downward,* giving it a *cap-like appearance,* while in others the opposite condition occurs, the edges being raised; as pointed out by the observer just mentioned these peculiarities are *unquestionably the result of inequalities in the strength of the different muscles composing the tongue.* The impression of the teeth is always marked on the edges of the organ.

The tongue remains in the intervals between the attacks unusually red, but the depth of the color gradually fades with the lapse of time. Lussana says that with a return to health the tongue gradually becomes smaller, less red, the fissures shallower, and the surface *paler;* to the pallor he particularly drawn attention, as it should not be understood that the organ returns to its normal tint, but acquires a *pale and anaemic appearance which is permanent.*

Beneath those areas where *ulceration* has occurred in the actute attacks *whitish* or *yollowish streaks* are frequently discernible, these being evidently caused by scar tissue beneath the mucous surface.

As the pellagrous condition grows chronic the condition of *papillary ptosis* described by Gemma gradually spreads itself over the tongue's surface, and the organ acquires a *slick appearance,* comparable to that seen on the backs of the hands following the ordinary pellagraderms. In such cases the tongue remains

shiny, with an absence in the main of the papillae which normally cover it, and when it is felt with the fingers gives rise to the sensation noted when scars in other parts of the body are examined in a similar fashion.

Beneath the organ the peculiar lividity already referred to is frequently encountered; in the areas so affected *minute hemorrhages* are not uncommon, giving rise to small rounded red ecchymoses which contrast sharply with the deeper livid tint of the surrounding surfaces.

The *principal change of the lips, cheeks, palate and pharynx*, and *one of great importance from a diagnostic standpoint*, is the occurrence of the *livid areas* to which general consideration has already been given.

On the lips this change begins with the mucous surface, becoming more pronounced as it is traced backward and downward, acquiring a deep tint as the gums are approached, and spreading itself over these structures, and also outward on the inner surface of the cheeks. On the palatine vault the lividity describes an arc corresponding to the line of union between the hard and soft palates, and curves downward on either side to the edges of the gums.

A similar change is seen on the vault of the pharynx, particularly near the median line, but radiating laterally. On the lower and anterior aspects and between the pillars of the fauces this lividity is also not uncommonly encountered.

In every instance this change is closely associated with *tortuous, dilated veins*, the larger of which can be made out readily with the naked eye, and on close inspection there may be discovered accompanying them yellowish lines which evidently represent fatty degeneration of the surrounding tissues.

Occasionally these purplish areas exhibit *epithelial exfoliation*, and in some cases actual *ulceration* with the concomitant inflammatory changes.

It is interesting to note that in some instances a *painful condition* develops along the slight protuberance which runs antero-posteriorly in the vault of the palate, and which represents the point of union between the bones of the opposite side; in some cases the bone actually *enlarges* and becomes quite tender on pressure. This condition is most common in hereditary pellagra.

Tremor of the uvula.—Tremor of the uvula in *old or hereditary pellagrins* is sometimes observed, the condition being comparable to the phenomenon of a similar character which is quite commonly observed in the tongue. In such cases the uvula may be seen to shorten, to contract concentrically, and the tip of the organ to retract in such a fashion that its free end becomes cup-shaped.

Chronic pellagrous angina.—Chronic pellagrous angina is a condition described by Gemma, and which is said by him to occur *after many repeated attacks of acute pellagra*, and which he regards as a *symptom of pellagrous cachexia.*

This morbid state, like the similar acute condition, develops by an *extension of the inflammatory process by continuity of surface from the altered mucous membrane of the mouth.* Clinically it is characterized by dryness, producing a frequent desire to moisten the throat, and in some instances more or less alteration in the voice, and when occurring on the livid spots so frequent in this malady presents the appearance of smoked meat. In some instances small vesicles form, which are not more than half the size of a millet seed; where the inflammation continues for some time, and there is considerable swelling, these elevations may take on an angular contour. With the exception of its chronicity the course of the malady is the same as that of the corresponding acute form.

On the vault of the pharynx in chronic pellagrins Gemma has described certain small rounded protuberances which he calls *pharyngo-palatine fimbriae.* These bodies occur in the vicinity of the median raphe, and vary in size from that of a millet seed to a grain of corn; they are of a reddish yellow color and are located amongst the venous arborizations which accompany lividity; they remain throughout life. Gemma compares them to lichen.

The course of the *pharyngo-uvula lividites* and concomitant alterations is *always chronic* and *is wholly confined to old pellagrins.* These alterations occasion a good deal of inconvenience, as the patient complains of pains and burnings and of difficulties in swallowing, which may last for months or even longer, and frequently produce annoyance out of proportion to their gravity.

PAROTID GLANDS.—It is stated by Pearson that the parotid glands are quite constantly enlarged in pellagra, and, as would naturally be inferred under such circumstances, there are *changes in the saliva.* In addition attention has been called by Zilocchi (1) to the fact that the optic thalamus, which shows profound alteration in this malady, contains a center which on stimulation produces salivation, a condition which clinical experience shows is not altogether uncommon in pellagra. In some instances the hypersecretion of the parotids is doubtless the result of reflex action from the lesions in the mucous membrane of the mouth, but this is by no means always the cause of an increased flow of salita in this disease, as it sometimes occurs when little or no alteration can be detected in the oral mucosa.

The *character of the saliva* appears likewise to undergo an alteration, as many patients complain that it has an excessively salty taste; however, whether this be due to an actual increase in its saline constituents, or to excessive irritability of the nerves of teste is not certain.

While periods of excessive salivation are occasionally encountered, on the whole Lussana and Frua are correct in the statement that in general the quantity of this secretion is below normal; these accurate observers affirm that they have tested the *reaction of the saliva* in hundreds of pellagrous women, and have invariably found it *acid.* In one case Neusser (1) also observed that the saliva was sour, and that it was *incapable of converting starch into sugar.*

Lussana and Frua assert that the saliva of pellagrins contained a *cellular element* which differs from that found in health. Normally they found oval or rounded bodies with regular outlines, while in pellagra these cells are much larger and present an uneven contour. It is evident that they refer to swollen epithelial cells.

STOMACH.—Since dyspeptic disturbances occasion many of the commonest and most annoying symptoms of pellagra, these phenomena were naturally observed and frequently discussed by the earlier writers on pellagra. As these phenomena however are in every way identical with those which have been referred to in considering the first stage of the disease it will not be necessary here to discuss them further than to repeat that they consist in *burning in the esophagus and stomach, pyrosis, a feeling of fulness after meals, belching,* and not uncommonly *pains in the neighborhood of the stomach and about the apex of the heart.*

Where symptoms such as have just been enumerated occur with great regularity in an organ it becomes *a priori obvious* that there must be pronounced disturbances in its functions, and investigation has abundantly shown that this is the case.

So far as the records go Neusser (1) appears to have been the first to call attention to changes in the stomach secretion, he having noted in his monograph published in 1887 that the gastric juice contains an abundance of *sarcinae,* and that *free hydrochloric acid is absent;* unfortunately he does not give details as to the extent of his work.

Considerably later, in 1891, Roncoroni (2), on the request of Lombroso, examined the stomach content in two cases of pellagra, and in both found *hydrochloric acid absent,* but *lactic acid present;* that a certain amount of fermentative action had occurred, however, was shown by the fact that a small amount of peptone was present.

The first series of analyses on anything like an extensive scale reported were those of Agostini (3) in 1893, who gives the result of his examinations of twenty-one pellagrins, sixteen being men and five women; they were all suffering from mild forms of pellagrous insanity. As a result of his investigations this great clinician comes to the following conclusion:

"The study of the chemistry of the stomach of pellagrins shows a notable degree of *hypopepsia* and *hypochlohydria,* with *catarrh* of the mucosa of the stomach and *weakness of its motor power* and its *innervation.* While in some instances the *total acidity was normal,* the average was distinctly *less than half this amount.* Likewise *hydrochloric acid* varied from *none at all* to an amount in some instances *above the normal,* but with an average of about *half the usual quantity found.* The *combined hydrochloric acid was about one-third the normal.* The stomach digestion was slow and insufficient, as would be indicated by the absence or diminished amount of hydrochloric acid, and a low proportion of pepsin and of combined hydrochloric acid. This is likewise attested by the fact that the *mucus was increased,* and that *organic acids, particularly lactic, were present.*"

The foregoing statement of the condition of the stomach in pellagra is so clear, concise, complete and admirable in every particular that it leaves little more to be said on the subject further than to remark that these results have been fully confirmed by succeeding writers. Papers on this subject appeared in Italy in 1894 by Camillis, 1911 by Preti and Pollini, Masserini, and Cecconi, and in 1912 by Valtorta (6), while in America an absence of hydrochloric acid was noted in the admirable articles published on the subject by Nisbet in 1909, Johnson in 1911, and Myers and Fine and Niles, in his monograph, in 1912. There is a general agreement among these writers that there is as a rule *absence or great diminution in hydrochloric acid,* with a *decrease in pepsin,* not uncommonly *absence of lab ferment* and *lab zymogen,* a condition of retarded digestion due to the weak zymotic power of the gastric juices, and a decrease in the motor power of the stomach. Some of these authors, notably Valtorta and Masserini, state that *lactic acid is rarely present,* while others have found it with considerably greater frequency.

It is noteworthy that Zilocchi (1) has called attention to the affect on the organs of digestion that probably results from the changes which are quite constant in the *great nuclei around the fourth ventricle.* in this disease, since it is well established that alterations in this situation may give rise to *vasomotor dilitation* in all of the *abdomnal organs,* particularly in the stomach, intestines and liver, and [illegible] the corpora quadrigimini are closely connected with *motility of* [illegible]*omach* at both of its orifices.

INTESTINES.—As already indicated, no symptom is more common in pellagra throughout all of the years of its earlier course than *constipation,*—a constipation that in some cases may be so severe as to occasion impaction of the faeces. During this period patients not infrequently exhibit the ordinary symptoms of *mucous colitis;* indeed it has seemed to the author that the extreme frequency of this condition in the Southern States must have some connection with chronic pellagra,—a conclusion that is strengthened by the general severity of the symptoms and the frequent occurrence of the peculiar nervous phenomena which are so common in the mild but very chronic forms of this malady.

In addition to the constipation, these patients frequently develop a diarrhoea shortly after the beginning of a pellagrous onset, and indeed in some instances this may precede the other symptoms. It should not be forgotten, as was mentioned in considering the earlier stages of pellagra, that some of these patients suffer from a *chronic diarrhoea* for many years preceding a frank outbreak of the classical symptoms, and that, indeed, not infrequently they are brought to their graves without manifesting any of the other symptoms which are generally regarded as typical of this disease.

Gemma is probably correct in assuming that the diarrhoeas that come on during the course of the acute outbreaks are in a larger degree the consequence of catarrhal changes in the intestinal tract, though Roussel was rather of the opinion that the condition is of nervous origin; the colicky pains, tenesmus, and muco-bloody stools that occur during this period clearly indicate that, however much such influences may operate, the trouble is largely the consequence of inflammatory processes in the intestinal mucosa.

After the patients become cachectic, and toward a fatal termination, the faeces not uncommonly become *watery* and are passed *involuntarily.*

The stools are almost invariably *alkaline in reaction,* and of an exceedingly foul odor, though in the milder forms the fecal mass may appear normal.

Microscopically *triple phosphates* are frequently found in great amount, and, in addition, the eggs of parasites in localities where they are common.

The food ordinarily appears to be *fairly well digested,* this being *particularly true of starches.* On the other hand remains of muscle fibers are not uncommonly seen, indicating the lowered digestive power of the stomach.

In this connection attention may be directed to the researches of DeGiaxa (1, 2), who showed that not only were the *protein constituents of maize badly digested,* but that the *presence of this cereal in the dietary seemed to exert a bad influence over the absorption of proteins generally;* thus he found that in three persons, each of whom received 108 grams of albumin and a diet consisting of maize and beans, 27.4 per cent. of the total nitrogenous material was passed with the faeces. Not only does this represent a considerable loss in the total amount of albumin ingested, but the presence of such a quantity

of undigested proteids in the intestinal tract must necessarily give rise to an enormous multiplication of bacteria, and thus could not fail to be indirectly the cause of autointoxication, and perhaps irritation of the gut itself.

The conclusion last referred to is fully borne out by the researches of Cuboni (4), who showed many years before the paper of DeGiaxa was published that the faeces of pellagrins contained a much richer flora than those of healthy people.

Agostini (5) states that *congenital hernia* is very common in the inherited forms of pellagra.

LIVER.—There is nothing in the pathological alterations of the liver heretofore noted to indicate any great alteration in the secretion of this organ. True, the viscus is usually considerably smaller than normal, but this is simply the result of a general state of inanition which is extremely common in pellagrins in their last days of life, and is not of such character as would probably greatly influence the composition of the bile. That the liver, however, *performs its function in a perfectly normal fishion is highly improbable,* but up to the present time we have no extensive observations of an exact character that would indicate just in what particular its secreting power is altered.

As respects the glycogenic function we have, however, the experimental researches of Lucatello and Malfatti, who published an interesting paper on this subject in 1901. As the result of the study of twenty pellagrins these authors determined that sugar could be detected in the urine in all but three cases where three grams of an 80 per cent. solution of cane sugar to each kilogram of body weight was given in 24 hours. They likewise noted that the urea in eleven of their cases varied from 10.41 to 19.51 grams, figures which are considerably below the average for Europeans. More recently similar experiments have been carried out by Nistico, who showed that in twenty-one pellagrins glycosuria followed in every case where 2:5 grams of sugar to each kilogram of body weight was given; in five out of eight cases a similar result followed when 1.5 grams sugar to each kilogram body weight was administered.

THE GALL BLADDER.—The gall bladder has been shown by the author to present frequently catarrhal changes, sometimes with partial sloughing off of the epithelial coat, and the extension of the inflammatory alteration deep down into its walls. In several instances where this viscus was opened and drained, the patients greatly improved, and, what was quite extraordinary under the circumstances, the constipation which in every instance had been obstinate was in a short time entirely relieved; unfortunately some of these patients again gradually drifted back to their former state, but in a majority of them the bowels continued normal for some years following.

Whether of any significance or not, it may be here observed that on opening the gall bladder in the cases just referred to the viscus was in every instance found filled with a light colored, very ropy bile, which undoubtedly contained much more mucus this is ordinarily the case.

PANCREAS.—The excellent digestion of starches and fats in pellagra would seem to indicate that the pancreatic juice is not greatly altered, a deduction which appears to have been first made by Neusser (1). In a disease, however, which so profoundly influences the metabolism of the entire body it is more than likely that some change occurs, and it would be a matter of much interest to have this subject thoroughly investigated.

Already Gatti (2) has made some observations along these lines, he having tested the urine for the Cammidge reaction in eighteen cases, and found it positive in thirteen. This unquestionably indicates a disturbance of function of this organ, and the subject should be further investigated.

THE KIDNEYS.—But little attention was paid to the condition of the kidneys by the earlier writers on pellagra, both for the reasons that the methods of examination at that period were very imperfect, and that but little change was as a rule observed in these organs post-mortem.

A. Verga (1) and Calderini (2) appear to have been the first to make systematic examinations of the urine, but further than to observe that this excretion was *light in color, not uncommonly neutral* or even *alkaline in reaction,* and that the *quantity is generally below the normal,* nothing of importance was ascertained respecting it by these observers. Somewhat later Morelli and Lussana and Frua added somewhat to our knowledge of the state of the kidney excretion in pellagra, these writers agreeing that the *specific gravity* of the urine is usually *decidedly low,* and that the *amount of urea is less than normal,* and is uninfluenced by the amount of nitrogenous material ingested. Occasionally *polyuria* exists, as in a case reported by J. G. M. Hammeau, but in general it may be said that this is rare except where a temporary increase is observed during nervous or hysterical attacks, which are not at all uncommon in this malady. As pointed out by Lussana and Frua, the quantity of the urine may also be greatly influenced by the occurrence of diarrhoea, which, in this as in other diseases, causes a great diminution in the volume of the kidney excretion, and a corresponding rise in specific gravity.

In one instance Morelli found *sugar* in the urine, but no other example of this has been encountered in the literature.

Lussana and Frua particularly called attention to the fact that they have examined the urine of over 100 pellagrins, and in *not a single instance was a trace of albumin found.* The experience of other writers is in general agreement with the conclusions of these authors, though Lombroso states that he found albumin twice in 110 pellagrins, while in six instances, where the ordinary reagents used for the purpose gave no reaction for this substance, *tube casts* were found in the urine on microscopic examination. Along the same line are the observations of Vassale, who maintains that *parenchymatous nephritis* with *hypertrophy of the left ventricle* is a not at all uncommon complication of pellagra. Lombroso (11) quotes Della Rosa to the same effect, the latter observer having noted evidence of Bright's disease in

nearly half of the cases coming under his observation in the Tyrol. This complication is certainly very infrequent in the southern portions of the United States, as the author has never in his entire experience noted an instance of the kind. Indeed it may be stated that in this region an antagonism between the diseases seems to exist in that they but rarely occur in individuals of the same type; Bright's with us is a disease almost wholly of the large, well-developed and fleshy male, while pellagra is preeminently a malady affecting the dyspeptic, lean and neurotic female, though it, of course, numbers many males of this type among its victims.

D'Ormea (2) has recently investigated the *functionating capacity* of the kidneys by observing the rapidity with which methylene blue is excreted, and as a result of these investigations comes to the rather surprising conclusion that the secreting power of the kidneys of pellagrins is actually *superior to that of the like organs of normal individuals;* in the latter about 100 hours are necessary for the complete elimination of the substance mentioned, while in pellagrins the average is about sixty-eight hours. In this connection it may be mentioned that Devoto (2) has made cryoscopic observations on the urines of pellagrins, and has determined that in general their *mollecular state is high.*

The nature of the kidney secretion in pellagra will be more thoroughly investigated when considering the subject of general metabolism.

Heart and blood vessels.—In the great majority of instances the heart's action in pellagrins is faster than normal, but its beat is correspondingly *weak,* and in an overwhelming majority of cases, at least in this country, the *arterial pressure* is decidedly below the normal. On the other hand, as pointed out by Strambio, the action of the organ may be greatly retarded, this observer having noted instances where the pulse was only thirty-four to the minute.

According to Lombroso (11) 75 per cent. of pellagrins, and particularly those who are young, show a *diminution in the cardiac dullness,* and the *beat of the heart* can be seen only with difficulty or not at all; not uncommonly the *apex impulse is lower,* and *further outward* than normal, being between the sixth and seventh ribs, two to three and a half fingers below the nipple. As a result of weakness the *heart sounds* are heart with difficulty. According to the author just referred to *hypertrophy of the left ventricle* is rather frequent in the aged, and *mitral insufficiency* with *dilitation of the aortic opening,* with consequent *blowing murmurs,* are not uncommon.

According to D'Ancona and Rondi *murmurs* are quite frequent in pellagrins, these authors having found them in 251 out of 343 pellagrins, 126 of whom were men and 125 women. These murmurs the authors think are the consequences of fatty changes and brown atrophy of the heart muscle, and are not due to anaemia or valvular lesions.

Within recent years a number of writers, among whom are Vassale, Alpago-Novello (4), Zanon (1), Mannini, and Zanon and Vadoni,

have observed in pellagra *cardiac hypertrophy and thickening of the walls of the blood vessels,* with *increased arterial tension.*

Atheromatous changes in the larger blood vessels sometimes occur, but it is not of sufficient frequency to be regarded as having any connection with pellagra.

Whether or not pronounced changes in the heart and blood vessels occur to any extent in American pellagrins is very doubtful; certainly nothing of the kind has ever been observed by the author, nor is he acquainted with any references to such alterations in our literature. Of course this statement should not be understood as denying the possibility of such occurrences, for nothing can be more certain than that the causes that produce cardio-vascular disease and those that occasion pellagra must of necessity not uncommonly operate simultaneously in the same individual, but the author would only be understood as asserting that for some unknown reason the two diseases rarely here develop together in the same individual. It may be again repeated that with us cardio-vascular disease and nephritis are almost wholly confined to large fleshy males, while pellagra is a disease preeminently of the thin, nervous and dyspeptic of both sexes.

BLOOD.—The first extensive examination of the blood in pellagra appears to have been made by Lussana and Frua, these energetic observers having made a large number of analyses to determine its density and its chemical composition,—particular attention being given to the amount and character of the albuminous constituents of the fluid. The only result achieved was to show that the serum of the blood has a specific gravity somewhat below the normal, and that it, as in other diseases of inanition and cachexia, is less rich in certain chemical constituents than is normally the case. From the foregoing these writers conclude that the blood must be more dilute and less rich in red cells than in health.

Confirmation of the deduction just referred to came with the articles of Seppilli (2) in 1882-87, who showed from an examination of fifty cases of pellagra, all exhibiting evidence of advanced lesions of the central nervous system, that in general, and particularly in women, there is a decrease in the red cells of 50 per cent. of the cases, and an even still grater diminution in haemoglobin. Following this many interesting papers on this subject by various authors have appeared, in which still other changes in the blood have been noted; among the most important of these are the articles of Agostini (1), Lombroso (11), D'Abundo, Lui (1), Lucatello (1), Fratini (1), Lavinder (1), Mai (1, 2), Alvisi, Hirschfelder, and many others; in this connection particular reference should be made to the very thorough and complete monographs on this subject by Carletti (1, 4).

For the sake of convenience the principal results noted by the various authors who have written on this subject will be separately catalogued; these results will be considered in the order in which the various articles first appeared.

Red cells.—Seppilli (2) in fifty pellagrins found decrease in red cells in 50 per cent., the cells varying from 3,800,000 to 4,500,000.

Agostini (1) in a number of insane pellagrins found decrease in red cells in 85 per cent. of cases in men; in 25 per cent. of cases the number was 4,000,000, and in 60 per cent. varied from 4,000,000 to 5,000,000. In more than 35 per cent. of the cases it did not reach 3,500,000, and in 50 per cent. it oscillated between 4,500,000 and 5,500,000. The red cells were pale, of varying size, with many microcytes and poikilocytes.

In 1892 Lombroso (11) gives in his book the results of the examination of eighteen pellagrins, hitherto unpublished, but made in 1871. In only one case the number of cells was 4,250,000, all the others being normal; as many of these cases were typhoid pellagrins and others were very ill, it is quite plain that these examinations are not to be relied on.

D'Ancona and Randi did not count the red cells, but a deminution was deduced by comparison of fields in 235 cases out of 343. Microcytes were numerous in thirty-six cases.

Carletti (1) found decrease in red cells constant, though very rarely pronounced. No change in form or shape except perhaps a slight increase in number of microcytes.

Fratini (1) examined seventeen chornic pellagrins. He found red cells usually decreased in number, and their morphology somewhat altered, just as in other anaemic and cachectic conditions.

Galesesco and Slatineano in thirty-one cases found the red cells varied from 3,000,000 to 4,000,000, with no change in morphology of any moment.

Lavinder (1) recorded fairly constant secondary anaemia, usually not severe, with corresponding qualitative changes in red cells.

Siler and Nichols (1) found as a result of their investigations that the red cells averaged 3,859,000 per cubic millimetre.

Maj (1) observed that the red cells change form and lose color in the grave forms.

Cesa Bianchi and Agazzi examined thirty-six patients, ten women and twenty-six men, and concluded that in the milder forms of the malady that there is a decrease in red cells, and an accompanying diminution in haemoglobin, and that marked changes only occur when the malady becomes severe.

Hillman examined the blood in twelve cases two or more times and found that the red cells averaged 4,750,000; the lowest count was 3,920,000.

Haemoglobin.—Seppilli (2) in fifty cases found that the haemoglobin varied from 50 per cent. to 90 per cent.; where the disease was not far advanced residence in a hospital for a time generally restored the coloring matter to the normal.

Agostini (1) observed very generally a decrease in the haemoglobin, and noted the fact that this substance is always in direct proportion to the specific gravity of the serum, which, as a consequence, is on the whole rather low, being in 75 per cent. of the cases from 1045 to 1064.

D'Ancona and Randi found in 343 pellagrins the haemoglobin as follows:

135	haemoglobin	of	51	—	60
84	haemoglobin	of	41	—	50
64	haemoglobin	of	61	—	70
37	haemoglobin	of	31	—	40
14	haemoglobin	of		—	30
3	haemoglobin	of		—	71

The greatest anaemia was observed in youth and old age.

Carletti (1) found a constant diminution in the haemoglobin, it varying from 65 per cent. to 75 per cent. as a rule. There is no constant proportion between this substance and the number of red cells, but the latter are generally about 1,000,000 greater than would be indicated by the haemoglobin,—giving a color index of from 75 to 80.

Galesesco and Slatineano in thirty-one pellagrins noted that the haemoglobin varied from 70 per cent. to 90 per cent.

Siler and Nichols found that the haemoglobin averages 81 per cent.

Cesa Bianchi and Agazzi (1) observed that the haemoglobin decreased with the severity of the disease in thirty-six cases.

Hillman in twelve cases found an average of 83.8 per cent. of haemoglobin, the lowest estimate having been 58 per cent.

White cells.—Seppilli (2) found the white cells normal.

D'Ancona and Randi noted in 343 cases that the white cells were normal in 275, and very slightly increased in sixty-eight,—this scarcely being sufficient in amount to constitute a leucocytosis.

Carletti (1) observed that the number of leucocytes varies, but nevertheless there is usually a slight leucocytosis. The proportion between the white and red cells varies from one to 362 and one to 824. With the exception that there is a *slight increase* of the *large mononuclears* and now and then an *eosinophilia*, the different kinds of white cells preserve their normal proportions.

Fratini found in seventeen cases that there was usually a slight leucocytosis, the highest count having been 11,418 in one instance. He was *unable* to find an increase in the large lymphocytes, but noted that the eosinophiles sometimes reached the proportion of 6 per cent.; this he looks upon merely as evidence of irritation of the mucous membranes, as it is well-known that these cells increase in response to inflammations occurring on epithelial surfaces in any part of the body.

Peserico found that the *neutrophiles* in pellagra varied from 67.4 to 53.7 per cent., with an average of 60 per cent.; these cells usually have from two to four nuclei, commonly the lotter number, and those with one or five nuclei are lacking, or are very rare. The number of *lymphocytes* is always in excess, varying from 34.4 per cent. to 26.1 per cent., with an average of 32 per cent.

Galesesco and Slatineano assert that there is usually a slight leucocytosis, varying from 9,000 to 10,000 per cubic millimetre in thirty-one cases examined; care was taken not to count the blood immediately after meals. The leucocytosis is the result of a *slight increase* in the *small* and *large mononuclears* and in the *polymorphonuclear cells;* however, there is *no typical picture, nor constant increase in any one of the different varieties of white cells.* The number of lymphocytes varied from 17 per cent. to 33 per cent., the polymorphonuclears from 55 per cent. to 78 per cent., the large mononuclears from 10 per cent. to 22 per cent., and the eosinophiles from 2 per cent. to 4 per cent.

Masini found that the *eosinophiles increase with the severity* of the process, but while still above normal, this change is not so marked in the *insane.* Despit confirmed these results in the *insane,* and observes that the *slight increase* is confined to the *lyphocytes,* particularly the *smaller varieties.*

Lavinder (1) found that leucocytosis is rare, and is probably not a phenomenon of uncomplicated pellagra. It seems likely that there is a *relative increase of mononuclears.*

Siler and Nichols (1) noted that in 67 per cent. of cases there was a greater or less leucocytosis; in 23 per cent. the white cells were normal, and in 10 per cent. they were below the normal.

Walker found the white cells slightly increased in four, normal in six, and slightly decreased in two cases.

Maj (1) examined nineteen cases and came to the conclusion that it is *not possible to enunciate a leucocytic formula for pellagra.* There was often an *increase in large mononuclears* and *intermediate forms,* and, as in other diseases, there is constant *eosinophilia* during the period of convalescence. Occasionally leucocytosis may be the consequence of intestinal parisites. *Leucopnoea* occurs in grave forms of typhoid pellagra, accompanied by degeneration of the white cells.

Cesa Bianchi finds in thirty-six cases that the *normal proportion* of red and white cells is maintained, with a slight tendency in certain cases to a *mild leucopnoea.* In all cases there is a marked *increase* in *large mononuclears,* with corresponding *decrease* in *polymorphonuclears. Lymphocytes were normal,* with a tendency to slight decrease. *Transitional* and *mast cells* normal, as are likewise the *eosinophiles,* except there is a slight increase in these where skin lesions are marked. The *changes observed are not charactristic of pellagra, but are simply the result of hibitual malnutrition.*

Bardin found that *tuberculosis complications* make a difference in the blood findings in pellagra; where the former disease occurs during the course of the latter the number of *polymorphonuclears is high,* and the *small lymphocytes normall or decreased,* while in the *simple cases* the *polymorphounuclears* are reduced,

the *small lymphocytes much increased,* and the *large lymphocytes slightly increased.*

Hillman in twelve cases found the *white cells normal* in six and *moderate leucocytosis* in the remainder; the highest count was 18,000. The most marked peculiarity of blood was slight *increase of lymphocytes* at the expense of the *polymorphonuclears,* the former running as high as 52 per cent. in one instance. Also a moderate *increase* of *large mononuclears* and *eosinophiles.*

Kozowsky found an increase in the both *small* and *large lymphocytes,* the *vacuolated* leucocytes, the *cells of Furex, disintegrating leucocytes,* and sometimes in the *myeloblasts,* the *myclocytes,* and the *promyelocytes.*

Iron content.—Lucatello (1) first showed that the *iron content* of the blood is relatively increased as respects the haemoglobin, the amount in some instances being double that present in the coloring matter. Carraroli (2) comes to similar conclusions.

Carletti (1) came to much the same conclusion, though he states that in some instances the iron *equals,* or rarely may be *even less* than would be indicated by the haemoglobin.

Reducing power.—Carletti (1) found that the capacity of pellagrous blood to absorb oxygen is sensibly less than that which will be taken up by normal blood.

Alkalinity.—Lui (1) found the alkalinity in pellagrous insanity *considerably below the normal,* the decrease becoming more pronounced along with the gravity of the affection, and returning again to the normal when the patient recovered physically, irrespective of any mental improvement.

Cappelletti came to a similar conclusion, finding in thirteen out of twenty cases the alkalinity lower than the ultimate limit considered as normal, and a still more marked decrease when the intoxication became grave; the alkalinity increases with the patient's improvement, and decreases during exacerbations.

Lambranzi in a somewhat more extended study of the *reaction of the blood* in various psychoses concluded that the alkalinity is below normal in dementia paralytica, and in epilepsy, during, a short time before, and after the attack, and it would therefore appear that *pellagra is the only psychosis other than dementia paralytica in which this condition is ordinarily found.*

Carraroli (2) found the alkalinity varies between 0.28—0.32 of sodium hydroxide.

Isotonia.—Agostini (2) in an examination of the blood of a number of insane persons found that the red cells of pellagrins showed the least resistance, this varying from 0.50—0.54, and even going as low as from 0.64—0.66. He observed that the resistance of the cells diminished always in those individuals in whom death was approaching, and that in those who were on the road to recovery there was first augmentation in the haemoglobin and the number of cells, with *increase of isotania following considerably later.*

Obici and Bonan made somewhat similar observations, though they found that the resistance of the cells was somewhat higher than determined by the previous investigator; the medium they found to be 0.40—0.42, while the minimum was 0.52—0.54.

Carraroli (2) found the isotonic power greatly reduced.

Carletti (1) has likewise investigated this subject, with similar results, he having found that the medium resistance instead of being 0.36—0.38, goes down to 0.46—0.48, or even lower.

Fluorescence.—It having been suggested that pellagra is related in its causation to the affection produced by the photodynamic poisons of buckwheat, Hirschfelder investigated the serum of both normal persons and pellagrins for the presence of fluorescent substances, and found that, while such bodies are present in the blood of the latter, the amount is not greater than in health.

Biologic characteristics.—D'Ormea (1) appears to have been the first to investigate pellagrous blood to determine as to whether it contains *precipitins, agglutinins* and *haemolysins,* but was unable to determine that it differed greatly

from that of normal individuals; not only was there no appreciable difference between the action of the serum of normal and pellagrous blood on that of various animals, but the converse was likewise true.

He, however, showed that the serum of pellagrous blood acts as a *precipitin* on the cellular plasma of the tissues of animals, and also that of other pellagrins (heteroprecipitins and autoprecipitins).

Carletti (4) likewise investigated this subject and determined that pellagrous blood has an *iso-agglutinating* power a little greater than that of the normal individual on the blood of sick persons.

This matter was also investigated by Besta (3) with entirely negative results. This writer is not of the opinion that the results obtained by anti-sera in the production of precipitins would, under any circumstances, be of very great significance, as he points out, as shown by Nuttall and Tshistowitch, that this phenomenon is only an accessory reaction of the organism to pathogenic agencies, and has no necessary connection with immunity.

In 1911 Carletti (4) again took up this subject and investigated *autocytoprecipitins* by using the extracts from various viscera of a dead pellagrin, and testing with the sera of five persons who were in the active stages of the disease, and five patients ill with other affections, with results that were extremely contradictory and unsatisfactory. Carletti inclines to the opinion that these results confirm the view of Centanni, who maintains that autocytoprecipitins represent the reactions of the organism against certain bodies produced by the diseased tissues, and, if this be true, it, of course, makes no difference whether the changes in the viscera are the consequence of one toxic substance or another. Mention is made of the fact that Lucatello injected the serum of pellagrins into rabbits, and found that the serum from their blood mixed with the serum of pellagrins produced a precipitate. Based on this observation Gosio and Palladino suggested a method of diagnosticating pellagra by determining as to whether or not the serum of the suspected individual gives a precipitate with maize extracts, but unfortunately where such reactions occur it would appear that they are to be looked upon as somewhat in the nature of a periphenomenon, as they seem dependent wholly upon whether or not the patient has absorbed maize albumins directly into the circulation through erroded or ulcerated surfaces in the gastrointestinal tract.

D'Ormea investigated the *haemolysins* of pellagrous blood, but was unable to discover any action of this sort differing from the normal. G. and S. Gatti however came to a contrary conclusion, having shown that pellagrous blood in all of the various clinical phases of the malady presents a *haemolytic power greater than the normal;* this is true not only of the globules of the same species, but of other species. They likewise assert that the serum of pellagrins is *never autolytic,* not even in the severest forms of typhoid pellagra, nor in the gravest conditions of organic misery.

In this connection it is interesting to note that recent investigation has clearly shown that *neither the Wassermann nor the Ascoli meiostagminic immunity phenomenon* is present in this disease, nor were Babes and Busila able to obtain agglutination of any of the organisms of the skin or intestines of pellagrins, or any of the organisms commonly found in maize when added to the serum of pellagrous blood; neither were these authors able to find evidence of complement fixation when they employed as antigens extracts of the germs just referred to, or those of the urine, dejecta, and skin of pellagrins, or of alcoholic and watery extracts of fermented maize. Alvisi has confirmed the observation of Carletti respecting the absence of Ascoli's phenomenon.

As first shown by D'Abundo, and later of D'Ormea (1), the blood of pellagrins possesses no greater *bacteriocidal power* than is normally the case.

Toxicity.—A number of investigations have been made with the idea of determining the toxicity of pellagrous blood, but the results have been so contradictory that the matter is still far from settled; this is doubtless the consequence largely of the inaccuracy and lack of delicacy of our methods of making this estimation, and even to a still greater degree to absence of any change in the blood itself.

The first investigator who took up this subject was D'Abundo, who came to the conclusion that the *toxicity of pellagrous blood is normal or but little in-*

creased, and he actually found it greatly lowered in one instance in eight. Practically contradictory results were obtained by Ceni (2, 3) some years later, who produced profound disturbance in the development of the chick by injecting the serum of pellagrous blood into the eggs, and afterwards observing the resulting embryo; this toxic power was particularly pronounced in the blood of typhoid pellagrins. Following this Besta (3, 6) and Carletti (4) instituted experiments, as the result of which they agreed with D'Abundo, while Gosio and Palladino and Antonini and Mariani (1) came to diametrically opposite conclusions. Not only did the last named writers show that *pellagrous serum is toxic*, but they demonstrated that the *serum of a cured pellagrin added to it neutralizes its poisonous properties*. They also showed that animals poisoned with maize toxines on recovery acquire a *certain grade of immunity* against the toxic power of the serum of active pellagrins. Likewise Babes and Manicatide showed that the toxic power of maize may be *neutralized by the serum of cured pellagrins*, and that this action is of a specific character.

Neusser (1) found no spectroscopic changes in the blood of typhoid pellagrins.

From the foregoing experiments to the curative injection of the *serum of healed pellagrins* into those actively suffering from the disease was, of course, a simple step. We find Antonini and Mariani (2) declaring that typhoid pellagra is decidedly benefitted in this way; S. Gatti (1) likewise observed similar results. Carletti (4) points out that Cole, Gilman and Winthrop and others have, however, claimed beneficial results in pellagrins by injecting *normal human blood*, and we should therefore be somewhat careful in arriving at conclusions before this matter has been thoroughly investigated.

It is of great interest to note that Ghirardini and Zuccari, and Volpino, Mariana, Bordoni and Alpago-Novello (2) have observed severe anaphylactia phenomena in guinea pigs inoculated with the serum of pellagrins after having been fed on mouldy maize for fifteen or twenty days; the former writers even say that death follows in twenty-four hours; the latter only got severe phenomena by injecting the serum into the peritoneal cavity.

LUNGS.—Ordinarily the lungs are not affected in pellagra, though as pointed out by Zilocchi (1) the lesions in the basal ganglia must necessarily more or less influence the respiration.

Now and then bronchitis is encountered, as pointed out by Gemma (4) and Roncoroni (1).

Fetid bronchitis.—The former observer has described a form of fetid bronchitis in pellagrins which pursues a chronic course. The disease commences ordinarily in the spring, with chilly sensations, a vague sense of pain in the limbs and arms, followed by a marked rise in temperature; these phenomena cease suddenly, and give place to a bronchitis, which usually develops during the course of twenty-four hours. In some instances the trouble may come on without chilliness, but with a rheumatic form of fever lasting from twenty-four to thirty-six hours, after which an abundant secretion of mucus from the bronchial tubes occurs. In still other cases there is neither fever nor previous pain in the limbs preceding the outbreak. For sometime after the trouble begins the tongue remains sticky, raw, and tremulous, and the individual is apathetic, lying upon his back with fixed eyes and complaining of no particular pain; the pulse is usually rather slow, and the temperature is normal or slightly subnormal; the patient is bathed in perspiration, and suffers from insomnia; the urine shows no change. While these symptoms continue the patient exhibits the symptoms of chronic bronchial catarrh, but

the cough necessary to expel the mucus is not fatiguing or very painful, and decreases toward morning. The catarrhal excretion is thin, has a yellow color, or is reddish from an admixture of blood. The disagreeable symptom above all others, and that which causes most discomfort, is the frightful odor of the breath, which is truly insupportable. Throughout the course of the trouble the respiration is fairly free, there being little dyspnoea. The physical examination shows the usual signs of bronchitis.

Sometimes this trouble develops in the spring, along with other pellagrous symptoms, particularly in those who have had the disease for a long time, and who have suffered from neuralgic disturbances.

The malady has a very chronic course, even lasting for months, but yields very readily to anti-pellagrous treatment. Left to himself, the patient gradually grows weaker and usually dies. In some cases the trouble seems to be benefitted with the coming on of warm weather.

Gemma does not consider this bronchial trouble as pellagrous *per se,* but only thinks it exceedingly apt to occur in pellagrous patients who have grown very weak.

He, of course, admits that other forms of bronchitis may also occur.

GENITO-URINARY SYSTEM.—Further than the rare development of *paralytic conditions about the bladder* the male genito-urinary apparatus seems to undergo no special changes in this disease. Disturbances of a similar character, of course, also occur in the female.

Irregularity in the menses is very common.

Not uncommonly *chronic catarrhal changes* occur in the *vulva,* and in the *endometrium,* which may or may not be coincident with the typical pellagrous attacks. These conditions need further study very badly.

Agostini (7) has especially directed attention to the fact that in hereditary pellagrins *menstruation is often delayed to the eighteenth year,* and in some cases *remains in abeyance throughout life.*

NERVOUS SYSTEM.—From the beginning it was recognized that pellagra is a disease in which the nervous system is more or less affected. Thus we find that Casal notes disturbances of sensation and motion, and mental alienation. Great stress was likewise laid on this phase of the subject by the great Italian pellagrologist, Strambio. With progress in the study of the malady interest in the nervous manifestations increased rather than diminished, particularly since the application of the more modern methods of histologic research has shown that the most important and severe of the lesions produced in this disease occur in the central nervous system.

Sensation.—From the reports of European investigators it appears likely that disturbances in sensation are more common in the old world than in the new, but it is perhaps rarely true that sensibility is profoundly altered. Exceptions to this however undoubtedly

occur, as in the case recorded by Casal, where the patient was unable to distinguish objects with his fingers.

The first accurate study of this subject was that made by Tonnini, who determined, particularly in the late stages of the disease, that *tactile sensibility* is diminished not uncommonly in the lower extremities; he also showed that now and then similar changes occur in the face, though in the latter case it is usually accompanied by similar disturbances over the entire body, which this observer considers as being the result of general weakness. He found in no case hyperaesthesia.

In a very careful investigation by Roncoroni (1) some years later it was determined that the *sense of touch was more or less diminished.*

Measurements with the aesthesiometer in twelve cases showed that on the tips of the fingers the average distance at which the two points of the instrument could be distinguished was on the right side 2.70, and on the left 2.85, and on the tip of the tongue 1.55 mm.

In a more extended study made some years later Albertotti investigated tactile sensation in the insane and obtained the following figures as the result of the examination of thirty cases of this kind:

	Pellagrins.	*Normal.*
Finger	2.2	2.1 mm.
Forehead	15.0	8.8
Back of neck	21.0	10.0
Back of hand	28.0	19.5

Thermal sensibility was found by Tonnini to be somewhat diminished in all stages of the disease, both in the extremities and trunk. In some cases a sense of pain results from the application of cold to the bodies of pellagrins.

Muscular sense was investigated by Tonnini with the result that no marked loss could be demonstrated.

Pain sense in pellagra was likewise carefully investigated by Tonnini with the result that he concluded that to both mechanical and electrical stimulation there is great diminution in this respect, particularly in the third stage of the disease; the alterations may be demonstrated in the legs, and to a less degree in the face. According to this author hyperalgesia is rare, particularly in the earlier stages of the affection. On the other hand *paraesthesia* is rather marked at this period, manifesting itself in *prickling, burning, rarely pruritis;* burning in the hands, feet and stomach, and a feeling of constriction, is more apt to come on at a later period. He likewise found that there is often vasomotor disturbances, with a *sense of coldness.* In the third stage there occur occasionally sensations *resembling the lightning pains of tabes,* though much more common are *neuralgias* of the intercostal nerves, and of those of the lower part of the trunk. In the first and second stages pains of a rheumatoid character are not uncommon in the legs.

Roncoroni (1) has also frequently observed *headache, ringing in the ears,* a *sensation of weight in the head, pain in the heels, violent neuralgia in the scapula and ankles,* all of which recur year after year, and are particularly troublesome in January and February.

Sensibility has been studied by Lombroso (11) by the electrical method devised by him for this purpose, with the following results:

On an average the spark from a Ruhmkorff coil is felt in the palm of the hand at a distance of 43 cm. in man and 60 cm. in woman, while in pellagrins the distance varied from 20 to 47 cm.; on the back of the hand the average in the normal is 55 to 61 cm., while in pellagrins it is 22 to 32 cm.; on the forehead in the normal it is 66 to 77 cm., while in pellagrins it is 48 to 64 cm.; on the back of the neck in the normal it is 39 to 49 cm., and in pellagrins 15 to 43 cm.

Somewhat more extensive figures are given by Tonnini, a copy of which follows:

	Medium in the Normal.	*Medium in Pellagrins.*	*Difference.*
Ball of the thumb	54	35	19
Forearm, internal surface . .	59	41	18
Forearm, external surface . .	60	35	25
Forehead, median region . .	92	90	2
Apex of the Nose	94	90	4
Apex of the tongue	150	146	4
Back of the hand	54	39	15
Palm of the hand	46	29	17

Lombroso remarks that in only one instance has he seen true *analgesia,* which occurred in a very robust and intelligent peasant; on the other hand he has frequently observed *hyperaesthesia* particularly marked on the abdomen and thorax, and which would cause the patient to cry out on the slightest touch. In other instances the patient was startled by the faintest noise. Some of these cases, according to this observer, have *burning sensations,* for which they pour water on their heads, and others complain of a burning in the eyes, nose, and face, and a feeling as though they were being stung by thousands of bees on the legs. He also noticed an *insensibility to cold,* and many patients, on account of a feeling of burning, exposed themselves voluntarily to temperatures ordinarily uncomfortable.

More recently Gregor has confirmed the increased sensibility of the skin in pellagra to faradic stimulation.

Eyes.—Disturbances of vision in pellagra are not at all uncommon, and have been recognized from the earlier periods of the study of this malady. Thus we find that Soler noted that the eyes of pellagrins often appear bleared, and that the cornea is frequently red and inflamed; likewise Strambio (4) referred to *diplopia* as being not at all uncommon, and says that patients frequently complain that their eyes are bad, particularly where mental disturbances are pronounced; he also observed *crepuscular amblyopia.*

So common formerly were eye symptoms among the pellagrins of Italy that Calderini (2) in his celebrated statistical study of over a thousand cases of this disease reported that 48 per cent. of the men and 72 per cent. of the women suffered from such disturbances of vasion as *amblyopia* and *diplopia*. Alpago-Novello (2) has observed the *arcus senilis* quite commonly in pellagrins.

The first observer who appears to have made ophthalmoscopic examinations of the eye was Guita, who, in 1884, reported that *retinitis pigmentosa* is not uncommon among pellagrins,—a condition which, on account of its resemblance to the excessive development of pigment within the nerve cells in pellagra, one would *a priori* suppose common in this affection, though it is probable that the coloring material differs in the two cases.

A year later Rampoldi confirmed the observation of Guita just referred to, and likewise mentions the occurrence of *hemeralopia, amblyopia, amaurosis,* and, in one instance, in a very cachectic pellagrin, he noted *atrophy* of the *choroidal pigment;* this writer also saw various affections of the *cornea,* such as *ulcer, necrosis,* and *parenchymatous inflammation* of its structure. He speaks also of *cataract* as not being rare in pellagrins, and likewise mentions *plus tension and sparkling synchysis* of the vitreous, combined with *crepuscular* and *nocturnal amblyopia;* this author also asserts that many cases of *opacity* of the *vitreous* can be ascribed to no other cause than pellagra. He regards *night blindness* as being a not uncommon complication of this malady.

Some years later Roncoroni (1) also took up this subject, and as the result of the examination of the eyes in 12 pellagrins found that the *pupil* of the *left eye* was *larger* than that of the *right* in two cases. In about half the patients also the pupils showed variations from the normal in *reacting to light,* there being usually a *diminution* which varied on the two sides. To *accommodation* the reaction of the pupil was *diminished* only in one case.

Somewhat later the same author (3) published the results of the opthalmoscopic examinations, which were made in three instances for him by Ottolenghi; in one case there was a mild *papillitis,* more marked on the left,—the center of the papillae being very white; the *field of vision* was more *restricted* on the *left* side than on the *right.* In the second case there was grave *atrophy* of the *papillae,* more marked on the left side, with displacement of pigment, advanced *optic neuritis,* diffuse *retino-choroiditis* in both eyes; the arteries and veins were small. The third case was normal.

In 1901 Bietti reported the examination of the eyes in ninety-eight cases of pellaga. In sixty-eight of these patients the results were negative, but in the other thirty there were observed *anaemia* or *hyperaemia of the papilla,* with *fulness* of the *retinal veins,* and sometimes *tortuosity.* Some of these cases examined post-mortem showed that the changes in the retinal veins correspond to a similar condition in the meninges. In *no* single case was there found *retinitis pigmentosa.* In one instance there was *atrophy of the papilla.* In sixty-five of the cases examined—that is in 130 eyes—the vision was

found normal in seventy-five, 20/30 in twenty-seven, 20/40 in fourteen, 20/50 in nine, and 20/70 in five. In none of the cases where the acuity of vision was diminished was there found a corresponding change in the fundus of the eye; on the other hand this condition was found to be due to *opacity* of the *cornea* or of the *lens*, to *astigmatism*, or to *advanced* age. The field of vision was entirely normal in fifty-five of the cases.

Microscopic examinations of sections stained by the methods of Nissl, Marchi and Pal showed no lesions of the optic nerve or of the retina,—the only alterations observed being slight changes in the cornea and conjunctiva.

Bietti stresses the fact that retinitis pigmentosa is purely an accidental occurrence in pellagra, and states that out of 230 cases examined by different observers the condition was not found in a single instance. He observes that the eyes in the pellagrous psychoses show pretty much the same condition observed in those suffering from other forms of insanity.

Very recently Whaley has made a most excellent contribution to this subject in his report of observations made on the eyes of 100 pellagrins; he found the vitreous humor *hazy* in four cases, *opacity* of the lens in five, *retinitis* in thirty-two, *neuroretinitis* in eleven, *choroiditis* in seventeen, *optic atrophy* in seven, *optic neuritis* in seventeen, *dilated pupils* in forty, *contracted pupils* in five, reaction to light *slow* in twenty-four, but *quick* in twenty-six, *photophobia* in eleven, *choked disc* in two, and *strabismus* in four. In every case where the examination could be made the *acuity* of vision was found to be defective, the eye-sight never being better than two-thirds of the normal.

In the same year Welton reported results of his examinations of the eye in pellagra. He found that the severity of the eye symptoms go hand in hand with the severity of the general clinical phenomena. *Cataracts* in an early stage are very common, as are also *inflammation of the retina and optic nerve;* still more frequent are changes in the choroid. Paralyses of the eye muscles occur rarely, and only in the last stages of the disease.

In a second paper Whaley has called attention to the fact that *eye changes are rare in children*, in whom pellagra is quite uniformly mild; he therefore infers that the absence of eye symptoms is of good omen.

Lastly attention may be called to the fact that Zilocchi (1) has observed that disease of the optic thalamus, which appears to be uniform in pellagra, is not unlikely a frequent cause of disturbances in the eyes, as it has been shown that irritation of this body has been found to produce *dilitation* of the *pupils* and *exophthalmos*.

HEARING.—In nine cases examined by Roncoroni (1) the sense of hearing was found lessened in seven and normal in two.

SMELL.—The sense of smell was investigated by both Roncoroni (1) and Lombroso (11), and was found normal by both; the author

has however seen instances where the sense was decidedly lessened, though such cases are apparently rare.

TASTE.—Roncoroni (1) was unable to detect any disturbance of taste, while on the other hand Lombroso (11) noted slight alterations; it was found by this writer that while solutions of sulphate of strychnine were perceptible to normal persons in dilutions of one to 500,000, and of sugar in dilutions of one to 80,000, the figures for pellagrins are respectively one to 243,000 and one to 37,000. In this connection attention may also be directed to the fact that a disturbance of taste in pellagrins is quite common in some parts of Europe, and is occasionally observed in America, as a consequence of which patients complain of a *salty taste of the saliva,* which is in all probability the result of disturbance of the gustatory nerves. Of like significance is the *bitter taste* in these cases to which Casal first directed attention (p. 330).

MOTILITY.—As was the case with the nerves of sensation, it was recognized by the earliest pellagrologists that there are profound alterations in the motor nervous system in pellagra, and we find constant reference to this subject in all of the clinical descriptions of this disease. In no way is this disturbance more commonly manifested than in the production of *weakness of the muscles,* going on in some cases to a condition of *paresis,* or even complete *paralysis.* Thus it was noted by Calderini (2) that there was weakness in the legs in 77 per cent. of the men and 83 per cent of the women he examined. At a later time the subject was very carefully and thoroughly studied by Tonnini. This writer called attention to the fact that in the earlier stages of the disease an *actual state of paresis rarely exists,* but that it is *not at all uncommon* in the *more chronic forms* of the disease, and is confined in both cases almost entirely to the legs; he notes that the respiratory muscles are never affected. Belonging to this class of disturbances are the *motor paralyses of the bladder* which occasionally occur in the third stage of the malady. While there are occasionally seen phenomena which are usually regarded as being the result of *vasomotor contraction,* and which commonly occur in the latter stages of the disease, more frequently there are encountered evidences of *vasomotor paralysis* even in the beginning of the trouble, and which may lead to *cyanosis* or *venous stasis,* and finally *edema,*—such cases having been observed by Calderini in 25 per cent. of his female patients; of like significance is also *mydriasis,* with a tendency to *drooping of the upper lid.*

Lombroso (11) also investigated this matter with much care and found that the arms as well as the legs showed a *diminution in strength,* and with a dynameter he found on examining fifty men and fifty women that the average with the former was twenty-seven and the latter nineteen kilogrammes. On the other hand this observer has noted cases where the strength was well maintained in the latter stages of the disease.

In this connection it should be noted that while pellagrins almost uniformly exhibit more or less *muscular weakness at all times,* the author has quite universally observed that this, as a rule, only becomes a *striking and important symptom during the periods preceding an outbreak of the external manifestations of the disease.*

In advanced cases a condition of *spastic paraplegia* occasionally develops, with all of the classical symptoms of this condition. Some years ago a case of this kind was seen by the author which was so typical in character that he felt little doubt as to the diagnosis; the milder symptoms of pellagra were for the most part wanting, or at least were denied by the patient, but a year or so afterwards the woman experienced a typical pellagrous onset, followed by death. Tonnini has noticed in these cases that the *muscular tension is greatly increased in the flexors,* and but little changed in the *extensor muscles.*

In severe cases of this kind *walking* may be seriously interfered with, or the patient may even become completely *paralyzed.*

As observed by Belmondo (1), the muscular disturbances lead to *difficulty in walking,* the gait of the patients being slow and uncertain, the steps short, and the knees are generally somewhat bent and the legs separated widely in order to give better support to the body; in many cases the patients require a stick in order to walk; often the sole of the foot is raised but little from the ground or even drags along its surface.

The *length of the tread* in pellagrins is generally *considerably less* than normal; as shown by Roncoroni (1) in eight out of fourteen cases the steps are further apart than usual, but in five they were nearer together than is ordinarily the case, while in one greater on the right side but less than the normal on the left; in six cases the left, and in seven the right foot, dragged more than normal, and in one instance both dragged equally. The angle of deviation was greater in six cases on the right and seven on the left.

It is noteworthy that in nine of fourteen of the cases which were examined by Lombroso with Roncoroni the gait was but little affected, the imprint of the foot normal, and the steps regular.

Dysphagia was found by Lombroso in 2 per cent. of cases.

Contraction of the palmar aponeurosis has been described by Parhon and Goldstein.

Tremor.—From the time of Casal irregular muscular action resulting in tremor has been recognized as common in pellagra. This writer gives *unsteadiness of the head and body* first place in his summary of the clinical phenomena of this disease, saying:

"An unceasing unsteadiness in the head, which, while it spares no one, is inclined to become so aggravated in some cases that the patients are unable to stand for the very shortest time without an irregular motion of the entire body" (p. 336).

Strambio (4) likewise observes that tremor may occur.

Belmondo (1) particularly called attention to *tremor* of the *upper extremities,* which manifests itself in quick, jerky contractions, which are increased on asking the patient to perform some action with his hands; the incoordination is likewise made manifest by having the patient close his eyes, and requesting him to perform actions with his arms and hands, such as touching the nose with the tip of the finger. Occasionally the *tremor extends to the head,* and is quite constant in the *tongue* in *hereditary pellagrins* during the active stages of the disease. Gemma (4) has noted a similar *tremor* of the *uvula.*

Roncoroni (1) found *tremor* in the hands in four cases out of eight.

In this connection it may be noted also that *Parkinson's disease* has been not infrequently noted as a complication of pellagra, and Paravicini considers that there is a connection between the two.

From the foregoing it would appear that *tremor* is *most frequent in Spain,* as Casal expressly states that all of his cases show this condition more or less, but that it is not uncommon in Italy. Babes and Sion (2) merely refer to its occurrence in Roumania, while Neusser (1), whose observations were carried on in Austria, says, "Trembling of the hands is rare in simple pellagra, and occurs still less commonly in the tongue."

It must be admitted that *pronounced tremor* is likewise *uncommon in America,* though it may be easily overlooked when it is not of a marked character; more or less tremor of the tongue however is not an unusual symptom in the disease as encountered here.

Gregor has observed *Romberg's symptom* in some instances.

Convulsions.—As the disease progresses and becomes gradually chronic other motor symptoms develop, consisting in well defined *cramps,* which are very painful, and which occur in the hands, legs and feet. In some cases they become so severe and painful in the muscles of the trunk that the patient is drawn backward; according to Babes and Sion (2) the occurrence of such cramps when very severe probably explains the cases of so-called pellagrous epilepsy. Ricci has recently reported a case of typical epilepsy in pellagra, which this writer thinks was produced by the pellagrous poison.

Choreiform movements are likewise occasionally seen, which according to Lombroso (11) manifest themselves usually in the early morning.

In pellagrous patients *irregular muscular movements* are not uncommon, there occurring sometimes clonic contractions of the muscles of the face and extremities, resembling in character quite closely the so-called electric chorea.

Tetanoid contractions are likewise occasionally encountered, as in a case mentioned by Tonnini, where this symptom even continued during sleep; high temperature developed as the spasms increased.

Lastly it must be noted that a *cataleptic state* is occasionally encountered in this disease, but this appears most generally to occur in the pellagrous insane.

Reflexes.—In general careful examination will easily demonstrate *profound alterations in the reflexes,—an exaggeration being more common than weakness,* as correctly pointed out by Lombroso. They appear first to have been studied by Seppilli, and later more thoroughly by Tonnini.

The mucous membrane reflexes are, according to Tonnini, usually diminished in the third stage of the disease; with this conclusion Neusser (1) and Roncoroni (1) agree.

The skin reflexes according to Neusser (1) are normal, but Roncoroni (1) in eight pellagrins found them only normal in two, exaggerated in five, and lacking in one.

The cremasteric reflex was examined in nine cases, and found lacking in three, increased in one, and in two exaggerated alone on the right side.

The tendon reflexes were found absent by Tonnini in some instances, but more commonly increased. In the cases investigated by Neusser (1) it was noted that the knee-jerk was increased in the majority of instances, in many normal, and in quite a number decreased; in a few the deep reflexes of the upper extremity were increased, while absent in the legs. In fourteen pellagrins Roncoroni (3) found the reflex exaggerated in seven, normal in one, weakened in two, in two diminished on one side but exaggerated on the other, and abolished in two. In forty-two cases Lombroso (11) found this reflex lacking in two, weak in three, and exaggerated in eight. In 300 chronic pellagrins investigated by Tuczek (3) the patella reflex was markedly *increased* in about half of the cases; in some instances a *patella clonus* could be produced by the slightest blow. In addition there was found a *dorsal clonus* in thirty or forty of the cases, and *marked increase* of the tendon reflexes of the upper extremities. In eight cases the knee phenomenon was entirely lacking, though there were absolutely no other symptoms of tabes. In the remaining cases the knee-jerk was either *normal* or *decreased. Differences* between the two sides was very common.

The foot clonus was found present in twenty-three cases in 300 pellagrins examined by Tuczek (3); in many instances the two sides differed.

Roncoroni (3) noted in his eight cases that the foot clonus was slightly present on one side in seven instances, and marked on both sides in another.

The Babinski reflex has been carefully examined by Duse in forty-three pellagrins, and he records that in twenty it was *marked* and in two *doubtful,* giving therefore a percentage of 46.22, which he points out greatly favors the assumption that degeneration of the crossed pyramidal tracts is common in pellagra.

Zanon (2) notes that the Babinski reflex appears to be of *prognostic value* in pellagrous insanities, as he has noted in 90 per cent. of cases of amentia presenting this symptom *resolution was tardy or a fatal termination occurred.* Associated with the Babinski reflex, but sometimes alone, this author likewise found *Oppenheim's leg phenomenon,*—the two signs going hand in hand with the pathological changes described by Tonnini, Belmondo, and others; these reflexes may prove at times of great diagnostic importance, inasmuch as they may make their appearance before other symptoms occur.

The plantar reflex was also investigated by this writer, who found that it exhibited *modifications of intensity* in 40 per cent. of cases.

In the forty-three cases examined by Duse the plantar reflex was *absent* in thirty-four, and in three cases the *Babinski reflex* was *present,* while the *plantar* was *absent.*

Zanon (1) further investigated this subject, dividing his cases into those suffering from their first attack of insanity, those who had repeated attacks, and finally the cases which had just stopped short of pronounced mental alienation. In the first class of cases he finds that the plantar reflex is *abnormal* in 60 per cent. of the cases, quantitative in twenty, qualitative in forty; in the second category there is constant *abnormality* of the cutaneous reflexes of the feet, there being qualitative alterations in 64 per cent. of the cases and quantitative qualifications in 36 per cent.; in the third class, although the writer only examined seven cases, he is convinced that the reflexes in the legs undergo a *constant modification* both as regards intensity and a variation in their character; he notes that in two of these cases the *plantar reflex is obtained in extension,* while in five cases it is *diminished while the leg is in a state of flexion.*

Roncoroni (1) found that in thirteen pellagrins *mechanical irritation of the extensors of the forearm* produced *mild contractions* in ten, and decided contraction in three.

It was noted by Neusser (1) that the *facial phenomenon* in pellagra was pronounced in a majority of instances, but *Trousseau's phenomenon* was invariably absent.

It was observed by Lombroso (11) that the *muscular tone* of the legs was *somewhat augmented,* manifesting itself in resistance to passive movement.

He also observes that *mechanical excitability of the muscles* is *increased.*

Sympathetic nervous system.—In concluding this phase of the subject attention should be called to the undoubted relationship which *disturbances of the sympathetic bear to pellagrous lesions.* That such an association exists there can be no reasonable doubt, since we everywhere see in innumerable directions evidence of disturbances of those nerves, which, united to the remarkable histologic studies of Foà, De-Giovanni, and particularly those of Brugia, leave no question of their being in all cases seriously involved.

Brugia examined the sympathetic nervous system post-mortem in thirty cases of uncomplicated pellagra, and found lesions in every instance. He definitely advanced the view that the *skin lesions,* and the *acetonuria* and *atonic diarrhoea* so frequent in the pellagrous insane, as well as the *constant dryness* of the *skin,* the *scanty perspiration,* and *alterations* in the *innervation* of the pupil are all assignable to changes in these nerves. With this view Tuczek (3) agrees. He regards the *goose flesh* and the *contraction of the blood vessels of the skin,* with *subjective* and *objective sensations of cold,* as being produced in this way; *local ischaemias* are to be accounted for in a like manner. In old cases there is often the opposite condition of *vasomotor paralysis,* giving rise to *capillary injection* of the *countenance*—particularly of the nose—such as is seen in old alcoholics, and quite frequently to *edema.* More recently still Mayer has advocated the probability of the *pellagraderms* being the result of changes in the sympathetic.

Cerebrospinal fluid.—The cerebrospinal fluid in pellagra has received careful consideration from a number of different observers. The first and most complete report of this kind was made in 1907 by Galesesco and Slatineano, who examined the blood and spinal fluid from thirty-one cases of pellagra,—twenty of which were the ordinary simple type, while the others showed either paralysis or mental disturbance. Most careful examination *failed to show any changes in the cerebrospinal fluid,* which these writers say is always limpid, and on being centrifugated shows only here and there a lymphocyte.

Some years later Bovori studied this subject, and likewise reports that the cerebrospinal fluid in pellagrins is *perfectly clear and limpid.* The tension of the fluid in the spinal canal is sometimes above and sometimes below the normal, being *elevated* where the nervous system is apparently involved, and *lowered* where the subject is weak, anaemic and cachectic.

The density of the fluid varies between 1004 and 1007; the viscosity from 1.14 to 1.28. The cerebrospinal fluid may present an increase of albumin (reaction of Nonne, and of Noguchi), and a slight lymphocytosis, along with an elevated testion. The trio of symptoms is an expression of meningeal irritation, and shows itself in those cases where the nervous system seems to be affected, even where the symptoms are slight. The cerebrospinal fluid contains no microörganisms.

Hindman likewise has written some interesting articles on this subject. In his latest paper he says that in a great majority of cases there is both an increase in protein content and cellular elements,—the former being more marked and constant. He finds no change in the fluid that simulates closely the alterations found in tabes, paresis and cerebral syphilis.

Still more recently Lorenz has made a report on this subject, he having examined 153 specimens of fluid from 106 cases of pellagra. His conclusions are as follows:

A *lymphocytosis* of the cerebral fluid does not occur in uncomplicated pellagra. *Globulin excess* of the spinal fluid is only occasionally observed. Lange's colloidal gold chloride test is uniformly *negative* in pellagra, as is also the Wassermann reaction, with but few exceptions; the exceptions were moribund cases which gave weak positive reactions with blood serum. The spinal fluid findings would seem to be *inconsistent with the conception that pellagra is an infectious disease of the central nervous system.*

From the foregoing it is clear that there is no change in the cerebrospinal fluid in pellagra of any consequence, and that, indeed, in the great majority of cases it is absolutely normal.

Electrical reactions.—Tonnini first investigated this subject, and found that with a faradic current the excitability of the flexors is

often greater than normal, but there is a notable diminution in the third stage of he disease in all of the muscles, even where they are spastic.

At a later time the subject was also studied by Roncoroni (2), who was unable to determine the *reaction of degeneration* in any of the muscles in four cases. In one case alone excitability was notably less than in the other pellagrins examined, which was doubtless due to the patients being extremely weak; however, not even in this case did the results vary beyond the normal limits. He found the *contractions of the flexors of the forearm were frequently greater than those of the extensors,* both to cathodal and anodal closing contractions, as well as to the faradic current. In some cases the contractility was equal in the two muscles, while in rare instances the *extensors gave more pronounced results than the flexors.*

On the other hand Gregor is quite in accord with Tonnini as to the marked loss of muscle excitability to the faradic current.

The foregoing results would seem to be of some clinical importance, inasmuch as one should be able to differentiate in this way between changes in the muscles due to a neuritis and those of pellagra; the method should likewise be of assistance in differentiating amyotrophic lateral sclerosis and progressive muscular atrophy from this disease.

Poychoses.—Disturbances of intellection are very common in this stage of the malady (See Pellagrous Insanities).

Temperature.—It is not uncommonly assumed that on the whole pellagra is an afebrile disease, but the results of accurate observation do not bear out this idea.

Nardi (1) seems to have been the first to direct attention to the frequency of increased temperature in pellagra, he having characterized the disease as a fever in a remarkable paper published in 1829.

More recently it was found by Bonfigli that eighteen pellagrins out of eighty-six had an elevation of temperature.

Somewhat later Roncoroni (1) made the interesting observation that the temperature sometimes varies on the two sides. He examined three cases for five days twice daily, and found that in two instances the temperature had a tendency to be slightly higher on the left than on the right. In eleven cases a single observation was made simultaneously on the two sides, and in five it was found higher on the left, in two equal on both sides, and in four superior on the right.

The most extensive and accurate observations on this subject however have been made by Alpago-Novello (2), who studied 100 pellagrins at the request of Lombroso.

The thermometer was placed in the axilla for fifteen minutes both morning and evening. Of the 100 patients sixty-three were men and thirty-seven women; two were under twenty years of age, thirty-nine between twenty and fifty, and fifty-nine in patients still older. Six of the patients were in the first stage, thirty-five in the second, and fifty-nine in the third. Control examinations were made simultaneously in ten patients suffering from afebrile diseases.

The number of examinations made in all was 22,274, and the temperature was found to vary from 95° F. to 106.7° F. (35° C. to 41.5° C.).

In 2,059 instances the temperature was above the normal, while it was below the mean in 5,251 cases,—the former being in the proportion of 9.24 per cent. and the second in 23.57 per cent.

Fever was found in the morning in 471 observations, or 2.11 per cent., while it occurred in the afternoon 1,588 times, or 7.13 per cent.

Only twelve patients showed at no time a rise in temperature; of these one was in the first, ten in the second, and one in the third stage.

The medium elevation of temperature in all of those patients showing fever was 100.33° F. (37.96° C.); while that of those patients showing a normal or lowered temperature was 96.82° F. (36.01° C.); the average of all of the observations made was 98.51° F. (36.95° C.), that is to say, it was something more than a degree less than the average of those having fever.

The observations on the ten non-pellagrous patients showed that only in twenty-two instances, or 1.36 per cent., was the temperature above normal, while in 774 instances, or 48.16 per cent., it was below normal in 1607 observations.

From the foregoing it was concluded that pellagra is distinctly a febrile disease, the temperature having been found sufficiently above the normal to constitute fever in 88 per cent. of the cases,—the elevation being more pronounced in the afternoon than in the morning.

In the six cases in the *first stage* of the disease the temperature was found above the normal in seventeen observations, or 3.82 per cent. of all examinations made. The highest temperature was 102.2° F. (39° C.), which occurred only once in one case. The mean for the entire period of observation in these cases was 98.09° F. (36.72° C.). Only one case showed a complete absence of fever.

In thirty-five cases in the *second stage* the temperature was above the normal 6.01 per cent. of the observations made,—that is about double the elevation showed in the first stage. The highest temperature observed was 102.9° F. (39.4° C.) in one case. The medium was 98.26° F. (36.81° C.). No fever was observed in ten cases, or 28.57 per cent.

Fifty-nine cases were examined in the *third stage* of the disease, and fever was found in 1,745 examinations, or 10.12 per cent. of all observations made. In one instance it reached 106.7° F. (41.5° C.). The mean temperature was 98.71° F. (37.06° C.). In only one case, or 1.7 per cent., was the patient without fever.

Not without *prognostic significance is the temperature* in this disease, as it is noted by Alpago-Novello that in the twelve cases which presented no fever at any time eleven left the hospital apparently well, and the twelfth was discharged no worse than when he entered for treatment.

Corresponding results were obtained where patients could be observed at different stages of the disease, that is, the temperature was found to augment as the sufferer passed from the first to the second, or the second to the third stages of the malady.

When the patients begin to improve the temperature gradually goes down, and conversely when the symptoms get worse the fever becomes higher. As a rule the fever becomes high for some days preceding death, though there are exceptions to this rule.

It is interesting to observe that very commonly an increased temperature does not occasion any subjective sensations to the patient, and that often it is unaccompanied by any exacerbation of preexisting symptoms, or by the development of new clinical manifestations. In rare instances the temperature goes down below normal as the patient grows worse,—Belmondo having observed a temperature of 86.05° F. (30.3° C.) in a patient under these circumstances.

Finally it should be especially noted that the *elevation of temperature* in pellagra is *eminently characterized by irregularity. Very rarely it is continuous,* and now and then it shows a *remittent tendency,* usually with evening exacerbations, but most commonly of all it is *intermittent.*

In the final stages of the disease the temperature not uncommonly appears to stay persistently *below normal* for long periods of time.

Third Stage.—The author's conception of the clinical character of what might be called the third stage of pellagra would include, in addition to the mild symptoms associated with the earlier periods of the disease and which continue throughout its course, one or more of the severer manifestations, which, instead of only appearing at intervals, now become constant; in other words the second stage becomes chronic. It may be here pointed out that this view respecting the third stage of pellagra does not materially differ from that of Roussel, to whom great credit is due for first conceiving the idea that, at least in a measure, the clinical phenomena of the later periods of the disease are due to organic alteration. According to his view the symptoms that occur in chronic pellagra are sometimes due to maize toxines, while in other cases they are the direct result of pathologic alterations in the various organs of the body produced by these poisons. He further assumed that a distinction may be made between these two conditions depending upon the presence or absence of pellagraderms,—these lesions being always the objective evidence of an acute intoxication resulting from maize toxines. According to the author's view this distinction is wholly gratuitous, there being no reason at all for assigning to the skin lesions a position of such overwhelming importance. Indeed, if it were the writer's intention to pick out any particular set of symptoms as being characteristic of pellagra his choice would centainly not fall upon the dermal manifestations, as the nervous phenomena come on earlier, are much more continuous, and are clearly of far greater significance than the alterations in the skin. There is no question that Roussel, like many other writers, has given an altogether unjustifiable prominence to the pellagraderms.

As according to the author's views the third stage of pellagra is the result of still more widely disseminated and more profound

alterations in the tissues of the body, we should naturally expect, if this conception be correct, that the symptoms in this stage of the disease should become correspondingly severe. Instead of the clinical manifestations only occurring when the patient's strength is taxed most severely—which is at the time of the change of seasons—we now observe that those organs and structures that have the lowest vitality and have suffered most, give rise to continuous morbid phenomena the year round.

Depending upon the nature of the clinical manifestations that are thus produced, various writers have described special chronic types of pellagra, to which presently brief reference shall be made. Before, however, discussing these peculiar forms of chronic pellagra the fact should be emphasized that in many instances it is difficult, and, indeed, sometimes impossible to assign specific cases of pellagra to any distinct clinical type. Not uncommonly two, three or even more of the pronounced pellagrous symptoms may occur simultaneously and with equal severity, making a classification impossible. On the other hand in not an inconsiderable proportion of cases the more characteristic manifestations may be present only to an exceedingly slight extent; under such circumstances the principal symptoms may only indicate a chronic cachexia with profound anaemia, or the patients may have simply an e aggeration of the nervous phenomena, but with no particular symptom especially prominent, so that it would be very difficult to determine as to whether motor, sensory or mental manifestations predominate.

In a very general way it may be said that it is rarely the case that the typical pellagraderms really become continuous, though the secondary skin alterations that result from the acute inflammations, being of a permanent nature, are of course often at all times discernible. Gastrointestinal symptoms are not at all uncommon in some cases, and often appear to be confined almost wholly to the mucosa of the mouth. Still more common are the nervous symptoms,—motor manifestations being particularly frequent. Mental changes, occurring alone, are not so common, at least those of a marked character, though when pronounced they should be looked upon as being usually indicative of very chronic forms of pellagra; apparent exceptions to this occur, but it may be doubted if they may not be after all only apparent. Chronic cachectic conditions are very frequent in this stage, but are usually associated with digestive disturbances. Profound anaemias are likewise observed, which appear to be unconnected with other and severe manifestations in some cases. Among the special types of chronic pellagra desribed by various authors the following may be regarded as sufficiently common to merit separate consideration.

Chronic gastroenteritis.—Chronic changes in the alimentary tract are not at all uncommon in pellagra, manifesting themselves simply as *chronic ulcerative changes of the tongue and mouth,* with but little or no discoverable alterations in the stomach or intestines.

In other cases there may be evidence of *chronic changes in the stomach,* giving rise to heartburn, pyrosis, and other digestive disturbances; in some few cases there is increased acidity.

In still other instances there is evidence of *intestinal disturbances,* usually manifested by prolonged *diarrhoeas,* which are apparently due to imperfect innervation, and perhaps to more or less catarrhal change in the walls of the intestine, and disturbances in the functionating capacity of the digestive glands; there is usually associated with this condition atrophy of the walls of the intestines, and ulcers are sometimes found in the large gut; in practically all instances the stools consist of a watery fluid, without the intermixture of blood or mucus to any extent.

Pellagrous amyotrophic lateral sclerosis.—Very commonly pellagrins show chronic symptoms that point unmistakably to *degeneration* in the *crossed pyramidal tracts.* At times the symptoms may assume in the most exquisite fashion the clinical appearance of amyotrophic lateral sclerosis; a very careful examination however under such circumstances will usually reveal slight disorders of sensation, associated with other pellagrous manifestations.

Tetany.—In rare instances *tetany* occurs during the course of chronic pellagra. Neusser (1) has seen instances where the disease occurred almost in epidemic form. It is most common in the insane.

Pseudo-meningitis.—At times clinical manifestations occur in chronic pellagra which have all the appearance of *meningitis.* Neusser (1) speaks of such a case, and the author has also seen one instance of the kind; unfortunately, as a post-mortem could not be obtained, it was impossible to determine as to whether or not an actual inflammation of the coverings of the brain existed.

Psychoses.—As already pointed out, the *psychoses* of pellagra are mainly confined to the latter stages of the malady, but usually come on as a sequel to a long-continued and pronounced pellagra, with classical symptoms. In some instances, however, pellagrous insanity develops before any of the other major manifestations of the disease have appeared, and may under such circumstances pursue an exceedingly chronic course, finally terminating in the most severe forms of mental disturbances that occur in this disease.

Essential anaemia.—The author quite agrees with Neusser (1) in the view that pellagra may give rise to a profound *cachexia,* in which the patient develops an *essential anaemia.* The author's cases have in most instances been women. They have been quite peculiar in that they have as a rule exhibited an *irregular, intermittent fever,* which in some instances has gone on for many years. At times, usually in the winter, these patients may be free of fever for several months at a time, but the elevations of temperature have uniformly come on again in the spring, and have lasted throughout the hot months. Occasion-

ally the temperature goes as high as 101° F. or 102° F., but as a rule it is much lower; generally speaking the elevation is slight, the temperature being usually from 99° F. to 100° F. in the afternoon, and as a rule below normal in the morning.

The blood examinations of these patients show a moderate diminution in red cells, with extreme decrease in haemoglobin,—this substance frequently being reduced to 25 per cent. or 30 per cent. of the normal. The blood picture is of course that of *chlorosis*, but most cases seen have been in women in middle life, and the blood condition has resisted stubbornly the usual means employed in the treatment of the disease just mentioned. Of significance in this connection is the fact likewise that the condition occasionally occurs in men, also in middle life. The leucocytes show no change, and the most careful examination of the red cells reveals only slight irregularities in size and form, with none of the appearances commonly observed in pernicious anaemia.

It is noteworthy that the skins of these patients are exceedingly pale, even when the blood returns, as it occasionally does, almost to the normal; it would seem that this condition is the result of a contraction of the small vessels of the skin. Two of the author's patients have developed scaliness of the backs of the hands quite regularly in the spring, but otherwise none of them have shown any of the major symptoms of pellagra, though all suffered with the digestive disturbances and minor nervous manifestations which are so common in this malady.

As the most careful examination has failed in every instance to bring to light any other cause for their troubles, these patients have been assumed to have the essential anaemic form of pellagra.

Chronic degeneration with consecutive atrophy of the organs.—A case of this kind has been described by Neusser (1), and the diagnoses was confirmed post-mortem. This is a condition which is closely related to the one just described.

Addison's disease.—It has been observed by many writers that pellagrous patients occasionally develop a typical form of *Addison's disease,* with corresponding changes in the adrenals.

Occasionally such cases develop independently of the other pronounced symptoms of pellagra. Neusser has seen cases of this kind in blond persons who were not malarious.

Paralysis agitans.—Pellagra sometimes manifests itself principally by the occurrence of symptoms that closely resemble those seen in *paralysis agitans.*

Thyroid disturbances.—Changes in the thyroid are not at all infrequent, particularly in hereditary pellagrins, and the lesions may manifest themselves by producing *goiter*, sometimes associated with *cretinism* and the corresponding mental changes.

Valtorta (5) has called attention to a form of *dysthyroidism,* in which the changes develop in this gland as a complication of pellagrous insanity. Under such circumstances the patient's mental state undergoes more or less alteration; there may be protracted *indolence, apathy, psychomotor paresis,* and a *profound torpor;* on the other hand the patient may present *inquietude, irritability, anxiety, bad humor, despair,* accompanied by *transitory edemas, constipation,* and *lowered temperature* in some cases, and in others by *diarrhoea, fever, tremors, arythmia* or *rapidity of the pulse,* and *exaggeration* of the *palpebral fissures.*

Pellagra sine pellagra.—As already indicated, the author thinks there is not a shadow of doubt of the very frequent occurrence of *pellagra without skin changes.* Not only may dermal alterations come on long after other major symptoms appear, but in a large proportion of cases no typical skin manifestations ever occur,—even in those instances where the disease reaches the second stage. The fact that pellagra may occur without skin lesions was noted by Casal, and was later fully recognized by the great master, Strambio, and in more recent times by Neusser, Babes and Sion, Lombroso and a host of others. The subject has been recently ably discussed by Lupu. It is noteworthy that Roussel was the only author of note of the last century who denied the occurrence of this form of the malady, but we should never forget, notwithstanding that he was one of the greatest of all pellagrologists, that he lived in Paris, and had but little practical acquaintance with this malady.

All doubt in this matter would seem to have been dissipated by the fact that the author has recently found all of the characteristic pathologic alterations in the body of a woman who died after a long illness with all of the symptoms of typhoid pellagra, with the exception only that there were no skin lesions of any kind.

PSYCHIC DISTURBANCES.

Mental symptoms may come on in any stage of pellagra, and, while commonly associated with the other classic phenomena of this affection, generally appear after the other symptoms have persisted for a time; as pointed out by Valtorta (1) psychic disturbances sometimes usher in an outbreak of the disease, in such cases almost always developing very suddenly and with great violence, leading quickly to a fatal termination.

Psychic phenomena are prominent throughout the course of pellagra, manifesting themselves in the early periods of the disease in *vertiginous sensations, loss of memory,* slight *mental irritability,* and *melancholy,* most pronounced usually in the spring, and, in the later stages, by these symptoms becoming more pronounced, the patient *crying and sobbing,* often imagining that he has committed the *unpardonable sin,* and as a consequence sometimes, though rarely, *seeks self-destruction;* along with these symptoms are almost always *loathing for food* and *mutism;* finally *maniacal* outbursts may occur. As pointed out by Lombroso, there is an *excessive moral impressionableness,* corresponding to motor excitability, and as a rule the victims are *more affectionate* than the average person. The *mutism* and *apparent stupidity* are often *only apparent,* and is thought by some never to be real in the early stages. The patient stands in *gloomy retirement,* often *without movement for long periods of time, seeks to escape notice,* and *flies from all social contact,*—often even *avoiding the light;* yet Lombroso well says

there is *not* an *abolition of the intelligence,* but a certain *stiffness of the mind.* In rare cases there is an *unusual gayety* and *increased mental activity.*

Sitophobia is exceedingly common, and *hydromania* is sometimes encountered.

In some instances the patient dies in the first attack, but more often after a period of from a few weeks to several months *recovery gradually occurs,* and there is a return to an almost normal condition; the mind, however, *never regains its former strength and elasticity.*

Usually in the *following spring* there is a *recurrence,* the symptoms being this time, as a rule, more severe; if recovery takes place there is a *repetition of the attack* as the warm weather comes on in the succeeding year, and this is kept up until finally the condition may become *chronic,* if the patient does not die in the meantime.

Most writers agree that in the latter stages a condition of *dementia* is usually reached, though it is maintained by some that this is only a *terminal incident,* the result of a profound intoxication, which has no real relationship to the characteristic mental changes in the disease.

The foregoing brief summary of symptoms together make up the clinical picture which most authors agree is characteristic of pellagrous insanity, but notwithstanding the subject's apparent lack of complexity it is as a matter of fact far from simple, and alienists have more than once engaged in polemics respecting certain disputed points in connection with it.

While fully recognizing that this subject is of no great interest to the general practitioner, the author feels that the clinical characteristics of pellagrous mental alienation are of very great importance from a diagnostic standpoint, and that the matter, therefore, deserves the fullest consideration of those who wish to investigate this subject thoroughly. For the convenience of all such, as well as that of the alienists, it has been thought advisable at this point to give as briefly as possible a résumé of the evolution of our knowledge of pellagrous insanity, and to place as far as possible before the American reader the views of contemporaneous European and American investigators along these lines.

In the summary that follows the author, hoping in this way to make a beginning in the very important matter of differentiating between the endemic forms of the malady and what he calls the parapellagras, has here only quoted those writers who appear to have been dealing with the former, and only such as have had actual clinical experience.

Constituting as it does one of the trinity of clinal phenomena most pronounced in this malady, this matter has naturally claimed the attention of all investigators from the time that the affection was first described. Thus we find Casal saying:

"For then many of those who are severely afflicted with *mal de la rosa* degenerate into mania or rather melancholia. And by this change the wretched patients, compelled not so much by madness as by intolerable mental and physical discomfort, are swayed by various kinds of trifles or notions. Leaving their homes they wander through the mountains and waste places, and, as not seldom happens, are inclined to lapse into a condition of desperation." * * * * *

"A fact which I have not infrequently observed will seem to some worthy of consideration, namely that very many of these who develop melancholia from this trouble die much more quickly than maniacs and melancholics who derive their illness from some other source." (p. 338).

According to Frapolli, the disease is characteristized partially by *melancholy* and partially by *mania,* and similar opinions are expressed by Gherardini, Fanzago and Rizzi.

Mental changes were likewise described by Strambio (4), who says:

"I would observe that pellagrous delirium may be either acute or chronic, and that both show certain peculiarities which distinguish them from all other forms of delirium."

"In the acute change, which rapidly leads to a fatal termination and is accompanied by an irregular fever, the patient is gloomy and speaks very little, though he may sometimes cry out in a loud voice; at other times he mumbles, shakes his head, or exhibits terrible fear, acting as though the most horrible spectacles were occurring before his eyes."

"The peculiarities of the chronic delirium are giddiness, religious melancholy, mutism, lycanthropy, a desire for death, and a tendency to commit suicide by drowning, which I have called hydromania."

"Others have noted that patients likewise complain of vertigo and dullness (ingrombamento) of intellect, and shooting, dull, fixed or vague pains in the head, but mention has not been made of certain peculiar cephalic sensations of which pellagrins complain, such as a noise like that made by a mill, or the striking of a hammer, or the ringing of bells, like a cicada singing, or the noise resembling that made by a sieve when grain is being passed through it." (p. 17).

The acute form of mental alienation of Strambio is unquestionably identical with that which more recent writers have called typhoid pellagra, and will be considered separately at a later time.

Calderini, (2) in 1847, appears to have been the first to make systematic examinations respecting the psychic changes that occur in pellagra, mentioning that vertigo develops in 75% of the men and 77% of the women; he noted delirium in 15% of his cases.

In the following year Verga (1) published what may be considered as the first serious study of this phase of pellagra, this being based on his observations in 7 cases. As a result he affirms that he *does not think we could seriously entertain the idea of this malady being identical with general paralysis of the insane.* In only one case was speech affected, and in none were there delusions of grandeur.

In 1849 Baillarger (2) published a paper in which he *sharply differed with Verga as to the possibility of pellagra's producing general paralysis,* stating that he himself had seen 12 cases of the kind, and that Bonacossa and Girelli had both observed similar cases.

In reply to the article of Baillarger and a criticism of the paper just referred to by the elder Strambio, Verga (2) again reiterated his formerly expressed views, but modifies his attitude to a certain degree by affirming that, while he has never seen anything of the kind, he admitted it might be possible that the same lesions that produce general paralysis under other circumstances might likewise in pellagra extend to those parts of the brain presiding over movement and give rise as a consequence to this affection.

According to this writer the pellagrous psychosis is characterized principally by *melancholy;* he mentions that the sufferer often expresses himself with a *profuseness of words,* pronounced in a bass voice, but *incoherent* to such an extent that it is not possible to construe their meaning.

Both Strambio and Verga were clearly of the opinion that general paralysis is entirely dependent upon the location of certain lesions in the brain cortex, and, as was natural considering the period at which they wrote, were clearly ignorant of the tremendous and probably all-important relationship that syphilis bears to this affection.

Many years later the view of Verga denying the relationship between pellagrous psychoses and general paralysis received strong support from Seppilli (1), who called attention to the fact that *general paralysis is exceedingly rare in the agricultural classes, in which the great majority of pellagrins are found.*

The subject of a possible relationship between general paralysis and pellagrous insanities was reopened in 1888 by the younger Baillarger, this writer maintaining, as did J. Baillarger, that the two diseases show many resemblances; he notes that in both the *paralytic manifestations are progressive,* but in each these *alterations remain incomplete* even until the end; likewise *hesitation in spech,* with *convulsive tremors of the lips,* and sometimes *inequality of the pupils* are found in both affections. He, however, admits that the *difficulty in speech* observed in pellagra is above all the *result of delirium,* while on the other hand in paresis this symptom is the consequence of paralysis of the tongue and lips, and this in his opinion constitutes the principal difference between the two affections.

This subject was again brought forward in 1897 and in 1901 by Pianetta's reporting in two papers four cases of supposed pellagrous insanity, with the *symptoms and usual changes in the brain that occur in geenral paralysis.*

The first article was replied to by G. B. Verga (2), who *strongly combatted the idea that there is any affinity between the affections in question,* though

admitting, as did the elder Verga, the possibility of general paralysis occurring independently in a pellagrous individual.

In addition Verga criticises the diagnosis in the three cases first reported by Pianetta, calling attention to the fact that two of the patients were women, one being 50 and the other 56 years of age, and suggested the possibility that in these two instances the psychosis might have been the result of the menopause, as it is thought by many that this is capable of bringing about the disease in question. He likewise objects to the third case, which was in a man 46 years of age, calling attention quite properly to the fact that Pianetta did not exclude the possibility of the disease having been due to the usual causes.

In this connection reference may be made to a paper by Brierre de Boismont, which appeared many years before, who likewise strongly deprecated the view that pellagrous insanity and general paralysis have anything in common. This writer is not however of the opinion that the mental derangement in pellagra is of such character that it could be regarded as constituting a distinct psychosis. He observes that it most frequently presents itself in the form of *lipemania*, though *mania* and *dementia are not altogether uncommon*. He considers that the stupidity which is so often seen in these cases presents striking differences from the similar condition observed in true melancholia. He observes that *mental derangements* ordinarily come on as one of the *rather late symptoms in pellagra*, but he has seen cases in which the opposite was true. A tendency to suicide he has not infrequently observed.

Clerici says that the pellagrous psychoses are never of that protean character described by some writers. They never become maniacal. The patients acts do not always correspond with the humor. Sometimes they talk and act like person drunk from alcohol. He has never seen a fixed idea of a well-defined character, nor constant hallucinations. The pellagrous insanities are characterized by a vertiginous delirium, vague, confused, accompanied by stupidity, loss of memory, silliness, and foolish talk. Sometimes the patient presents a sort of automatism, and in other instances develop a religious monomania. All of these mental states fluctuate from time to time.

Tamburini (2) has reported a case where a man became a thief during an attack of pellagrous insanity.

Bonfigli (2) was of the opinion that the pellagrous psychoses are characterized by a *wandering delirium, confusion, agitation*, and a *certain melancholy, hallucinatory delirium*, and *incoördination* of *ideas* and *motion*.

The distinguished Austrian pellagrologist Neusser (1) says that the pellagrous insanities are characterized usually by *melancholy*, and rarely by *mania*, and terminate usually in complete *dementia*.

Some years later Alpago-Novello (2) wrote a very suggestive article, in which he maintained that the pellagrous psychoses present the characteristics of a *precocious mental senility*.

Hagnal has seen instances of typical *mania*, as has also Mayer, who has observed instances of *typical circular insanity*. *Imbecility* and *dementia paralytica* have also been observed by the latter, and he has also exceptionally seen *epileptic* attacks. The psychosis is principally characterized however by *marked mental depression* and *profound melancholia*. Characteristic for these insanities is likewise the fact that the patients have a well-marked insight into their condition, and are aware of the fact that they are sufferers from a serious malady.

Righetti found *disorientation* common; the patient thinks he is at home, feels well, but is subject to *hallucinations*. He thinks some patients develop *true mania*, and is an advocate of the *polymorphic character of the pellagrous psychoses*.

Zlatarovic believed in the polymorphic character of the pellagrous psychoses; he saw cases of typical melancholia, and dementia, with complete stupor and loss of psychic functions. He saw no mania. He appears to have been the first to call attention to the *involvement of the thyroid*, with the consequent mental disturbances in this disease.

Warnock (1), who studied the disease in Egypt, is of the opinion that the pellagrous psychosis is akin to *melancholia*. Toward the end *hallucinations* develop, disorders of *smell* are most common, and melancholia changes to *dementia*. The author is of the opinion that "the form of *insanity occurring with pellagra*

is one peculiar to it, and is not simply the mental expression of the incidental cerebral malnutrition and anaemia. The apparent early occurrence in pellagra of symptoms of *dementia,* with *loss of memory* and *childishness,* points he thinks to *organic brain disease,* and this condition is comparable to similar lesions in organic dementia due to gross brain lesions, and to the morbid changes of the later stages of general paralysis.

A. Marie (1) has likewise made some studies of pellagrins in Egypt. He says that the insanities of these patients is characterized by an *initial period* of *irritability, asthenia, mental* and *physical apathy* and divers *delusions of fear; sitophobia* is also frequent and corresponds to the gastrointestinal troubles, *mutism* often occurs, and not infrequently the patients become *violent, apprehensive, avoid social contact,* and *hide in dark corners.* The *mental torpor* is accompanied by *lack of memory, spasms, vertigoes, epileptiform convulsions,* and their *psychic equivalents. Ambulatory automatism* is not infrequent, while *auto-accusations,* and *nosophobic* and *hypochondriac preöccupations* are not very rare, associated with vague *ideas of persecution.* The *stupor alternates with automatic raptures* and *with divers freaky ideas,* with or without an *attendant delirium mixed with dreams.* The *sitophobia* may be simply *due to a difficulty in swallowing,* or *may result from a lack of appetite,* or an *apathy bordering on katatonia;* it sometimes gives place to *sitomania* as a further phase, or the pellagrous insanity frequently assumes a *chronic form,* with or without *intercallary intermissions.*

In the *last stages of the disease, where paralysis has occurred,* the patient may present a condition *identical clinically with general paralysis of the insane.*

In his excellent treatise on pellagra the same author observes that the other characteristic symptom in addition to sitophobia is *hydromania,* leading not uncommonly to suicide.

This author likewise calls attention to the *intermittent character of the pellagrous psychoses,* the conditions improving during the colder months, to come on again as warm weather approaches. This is well shown in the following table, and represents statistics dealing with 100 pellagrins.

	Jan.	Feb.	Mch.	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
Attacks Developing	33	34	27	50	54	67	77	88	46	81	66	48

Mention is likewise made of the fact that the *symptoms* sometimes show *periodicity*—a *tertian type* not being uncommon. It has also been noted that the *manifestations are more pronounced* during the *hot* period of the day.

Babes and Sion (2) have likewise given this matter some consideration, and have described the mental manifestations of pellagra as the disease occurs in Roumania.

They say that as a rule the mental affection begins with a certain *sadness, uncertainty,* and particularly *weakness of memory.*

After the delirium begins the patients remain *weak,* with *indisposition to exertion of all kinds, melancholy, sad* and *weak* without cause; they are *greatly troubled about their condition.* The *delirium* or a *high degree of melancholy recurs yearly at the same period,* and with each attack the *intelligence suffers more and more,* and there is gradually produced a condition of *dementia.*

The *pellagrous melancholia shows different stages,* there being in the beginning an *inability quickly to grasp ideas,* followed by *apathy,* which progresses to *complete loss of intelligence.* Along with these there occur *delusions* of such character as to make the patient *think that he is being persecuted,* that he has *committed sins,* or they may take a *religious turn,* and along with which there are very common *hypochondriacal manifestations of all kinds.* The patients have a peculiar *mistrustful, anxious, absent look about their faces,* with which there is often combined an *appearance of dread.* Now and then, though rarely, *typical manic-depressive insanity occurs.* There are also cases where the patient has *resistless impulses* to commit certain acts; likewise *cataleptic symptoms, distortion of the countenance,* and *auditory delusions* are not uncommon.

In the *paralytic stage,* after the patients have become very weak, there occurs a certain euphoria, which closely simulates the clinical appearance *presented by*

dementia paralytica, and in fact the disease may be actually *changed into this condition at times.* The authors observed that even in the different stages of the disease *remissions occur,* and that if the patients under such circumstances are properly looked after a *complete recovery* may follow.

It is clear from the foregoing that these writers are convinced of the *polymorphic character* of the pellagrous psychoses.

The more accurate study of the mental symptoms of pellagra may be said to date from the publication of the works of Finzi in 1901 and 1902, as this author appears to have first given the subject thorough and careful consideration. This writer takes the position that the principal and striking characteristic of the pellagrous insanities is that there is a gradual loss of intellect until the patient gets into a condition of true *amentia,*—the word meaning in Italian confusional insanity. He says:

"The *mental symptoms* are not to be distinguished from other forms of *confusional insanity,* they *vary,* are *inconstant,* and exhibit *essentially exaggerated emotions.* Such *depression* as exists is found almost entirely in the *prodromal* and *convalescing periods,* and *do not belong so much to the psychosis* as it is the result of a normal mental impression and logical reaction to the unhappy social and physical condition of the patient."

"The pellagrous amentia takes on rather rarely a true and proper form of *delirium;* it presents itself on the other hand usually as a slight *confusion* and *lasts relatively long* (3 months). The *prodromal period* is also *very long;* also *long,* but not more than in other forms of amentia, is the *convalescence.* The *climax of the malady* is represented by *simple mental confusion, agitation,* and *asthenia,* according to my cases. Vary rarely there are *confusional hallucinations* and *stupor.*"

Agreeing with Finzi the celebrated Italian alienist Tanzi is likewise of the opinion that the *pellagrous psychosis is chiefly characterized* by *confusional insanity.* He says:

"A pellagrous melancholia has been described as the most common psychosis resulting from poisoning by bad maize. A pellagrous mania has also been described. The *characteristic psychosis of pellagra* is, however, *confusional insanity,* which *manifests itself acutely* in *loss of sense of place, loss of memory, confusion, hallucinations* and *paraesthesias,* from which there arise *morbid sensations* and *delusions.* Pellagrous amentia often assumes a *depressive form* which *simulates melancholy,* and in some cases is from time to time or throughout the whole course of the psychosis itself *accompanied by exaltation,* which gives it some resemblance to mania."

The writer lays stress upon the fact that the *first attack* usually occurs *after the patient has suffered from chronic pellagra for many years,* but notwithstanding this the mental change corresponds exactly to the most typical of the acute insanities, both as regards symptoms and course, i. e., *confusional insanity.* If the *patient be properly nursed,* and *particularly if he be well fed,* the *attack* is *usually not severe,* and *passes away in a short time;* not only is it necessary that the patient should be well looked after during the actual period of the attack, but it *is also essential that every attention be given to him during the intervals.* Where the patient goes back to his former method of life all of the symptoms, including those of a mental character, take on a more severe type, and we have the reparable lesions of *confusial insanity* replaced by the *irreparable alterations of dementia.*

The insanity of pellagra is then different from common melancholia or ordinary mania, and is also something more than simple amentia. He regards it as the combination of two distinct clinical pictures, namely, that of *confusional insanity* in the first attacks, and that of *dementia* in the latter and more pronounced phase, in combination wih a *chronic* and *incurable cachexia.* It is an *intermittent* and *progressive amentia* which, if not fatal and not cured in its earliest stages, terminates in dementia. Death not uncommonly occurs in the latter stages before a state of dementia is reached, the patient under such circumstances dying in a state of acute delirium.

That pellagrous patients, even when they show depression and exaltation, are not true melancholics or true maniacs may be inferred from many signs. A

pellagrous person when depressed has never the lucidity of the non-delusional melancholic, and his errors of judgment hardly show the *characteristic coherence of melancholic delusions.* When *exalted* he *displays more fear than rage,* more *confusion than gayety.* Beneath the depression or exaltation there can be readily discerned the confusion of amentia, even though it may not be chaotic. The patients internal perceptions are altered by the paraesthesia, and his external perceptions by the hallucinations, and the zone of images is confused by the direct disorder of the ideational process independently of affective disturbances.

In melancholia errors of judgment are less marked and less constant, and represent the secondary result of some disturbance of affectivity and moreover the *pellagrous subject* is always *dreamy, forgetful* and *stupid.* It is *only rarely that he can give an account of his past history,* that *he knows that he is in an asylum,* or *can recognize with promptitude* and *accuracy* the *doctors in attendance.* These victims of pellagra, humble representatives of the poor, speak only of their misery; they refuse to eat food from fear of suffering painful consequences, and they are suspicious of the modest but unaccustomed comforts that surround them in hospitals or asylums. Often they are tortured by the *delusion* that they are *damned.* In other instances they show extreme *humility,* or may exhibit *delusions of grandeur* that excite pity on account of the triviality of their nature; the possession of a sack of potatoes, a farm, a new coat, or a choice cigar constitutes the height of their ambition. Pellagrins are as a rule depressed and dull-brained, they speak little and in a low voice, and their appearance suggests dejection and resignation. The short duration of the attack of acute insanity is also evidence that the condition is one of amentia rather than of mania or melancholia.

This state of *intellectual degradation really begins in the first years of the pellagrous state,* and is evidenced by a tendency to melancholy and loss of memory; by the third or fourth year of the disease the confusion has greatly increased and the patient manifests *true delusions,* accompanied by changeable *sitophobias, sobbing, weeping, impulsiveness* and *agitation.* As a rule, however, the agitation is brief and is quickly followed by a further attack of depression, with immobile taciturnity and great increase in mental confusion.

Sometimes the *pellagrous psychosis* assumes the form of a *pseudo-progressive paralysis,* accompanied by *euphoria* and by some of the *motor symptoms* of this classical disease. For the completion of its clinical picture ordinary pellagra provides various characteristic symptoms, such as *rigidity of the pupils, exaggeration of the knee-jerks, bradylalia* (although more of mental than dysarthritic origin), as well as *amentia* and *dementia* to complete the resemblance.

The victims of pellagra may live for ten years or so manifesting every spring a fresh exacerbation of their disease. Their *physical* and *mental decadence* is in *many cases extremely slow.* The attacks naturally become more and more serious every year, and at last are accompanied by cachexia and dementia. *Ultimately death occurs, in spite of all treatment,*—resulting in many cases from pleuro-pulmonary tuberculosis (especially in children), bronchial pneumonia, interstitial tuberculosis, or scurvy.

Strongly differing with Finzi and Tanzi, Vedrani (1) has within recent years written very important articles on the pellagrous psychoses.

Very properly this writer begins a discussion of this subject by pointing out the imperative necessity in the beginning of each case of deciding as to whether or not the trouble is really pellagrous . He refers to the fact that pseudo-pellagraderms may be seen in the course of many different affections, and may frequently give rise to grave errors in diagnosis. He particularly calls attention to the writings of Garbini (2) in this connection. He refers to one of the cases of this observer, as well as to two of his own, all of which strongly simulated pellagra, but which on close investigation were found to be unquestionably dementia praecox; he mentions that another case with typical skin lesions turned out to be the result of alcoholism. Following Belmondo and Pieraccini, he calls attention to the *great resemblance clinically between typhoid pellagra occurring in the course of pellagrous insanity and delirium tremens.* The writer particularly emphasizes the fact that in alcoholic psychoses the conscience of personality is in a great measure preserved, just as he maintains is the case in the pellagrous

insanities, and we find also in the latter, where the paretic condition will allow, that peculiar motor restlessness which is so characteristic of the former.

When erythemas occur on the backs of the hands, as not uncommonly happens in both conditions, it becomes often a matter of extreme difficulty to distinguish between them.

There now follows a résumé of the mental peculiarities which Vedrani claims are characteristic of the pellagrous psychoses.

According to him the mental state varies greatly in different pellagrins. The invalid may lie under the weight of a *sadness* which cannot be comforted; another may suffer from a species of *dread*, with *abundant tears;* a third from a *mute despair*, or break forth from time to time in words of *sorrow* and *tragic wailing;* another is *anxious without sorrow*, accompanying which there may be a simple *uneasy restlessness* with *lucidity* of mind, or a more *violent anxiety* with apparent *fear;* in some cases there is a feeling of *well-being*, the patient lying upon the bed in a torrent of *laughter* and *gayety*, or finally the sense of happiness may be mixed with *anxiety*, such as Kraepelin mentions as being not uncommon in delirium tremens. These states of mind, however varying in the different pellagrous insane, *show but little tendency to change in the same individual*, though it is true that there may be alterations in intensity; patients observed by the author for three years have continued along the trend noted in the beginnnig. Vedrani calls attention to the fact that the foregoing is quite contrary to the statements made by authors as to the patiens with dementia and general paralysis, in which repeated and violent alterations of mental attitude occur. If the stability of the mental characteristics in insane pellagrins has shown in the author's cases differences from the condition observed in dementia and progressive paralysis, in another respect they exhibit marked similarity in that the *trend of the emotions is in harmony with the nature of the deliriant idea.* On the other hand in dementia praecox all consonance between the character of the idea and the emotional manifestations is broken; for example, the patient will speak with apparent indifference and with laughter of the most horrible crimes. Also in that form of alienation which authors call dementia there need not always be harmony between the emotional manifestation and the fixed idea; for example, Meynert, in his chapter on this affection, begins with the story of a woman who went into a violent rage because she dreamt she struck a frog. On the other hand in Vedrani's cases of the pellagrous insane the *sentiments correspond always with the idea;* the patient feels well and declares he is a lord; bewails desperately, and says he can never more breathe, that he cannot pay his debts, or that he is a mad-dog; another is crazed with anxiety and wishes to change his residence, for he says that everything has been stolen from him; another complains of debility, that he will never get well, and only awaits death.

The *deliriant idea in the pellagrous insane is multiform.* The individual is a rich lord, or has lost everything, he has yielded to sin and knows nothing but evil and treachery; another has cheated a child and makes the confession too late, is damned, has poisoned everybody, has given the key of Paradise to the devil, or has turned God over to the same malignant being; the doctors and nurses have stolen everything, the son and husband has been thrown into prison, or must be killed at twilight. In many cases the patients who *perceive correctly that which occurs around them* ascribe to themselves, in a manner *varyingly delirious*, that which others do and say; for example, case No. 8, seeing this observer writing his clinical diary, thinks that he makes a record of his (the patient's) debts, and says, "Write and mail it to the poor fellow, I have nothing with which to pay." In the main the *deliriant ideas lack clearness*, and it would appear that the *mentality is confused;* at any rate their expressions are vague; for example case No. 1 says, "You will see that they will certainly kill me at twilight." (Who?) "I will have many things which will kill me." Often the patient will admit that what he has just said is untrue. In general the *deliriant idea is a mobile element in the clinical picture;* what is maintained to-day may be forgotten for a long time, and either taken up again or something else substituted for it.

However, throughout the various perturbations of the mental state and of the deliriant phantasies this is noteworthy; there is a *consciousness of the ego*, the sum and substance of the mental processes through which the psychic and

corporal personality are recognized, not uncommonly *orientation* for time and place, and *memory* for recent and long past events are *never lost entirely;* commonly these characteristics are admirably preserved; above all the invalid has the consciousness of a grave malady destroying both body and mind, and he accuses it by name to the doctor, calling it the "accursed pellagra."

Vedrani then goes on to record examples of the words and actions of a number of his patients, all of which go to show that these poor unfortunates preserve during their most violent mental perturbations a correct idea concerning their personalities, their surroundings, and the identity of those with whom they come in contact; they are likewise perfectly lucid as regards recent and remote events and the nature of their disease.

This author asserts that it often happens that patients with pellagrous insanity *understand everything that has passed around them even where they have gone for hours, days,* or *greater lengths of time without responding to questions, and giving the impression of being affected with stupor, total eclipse of consciousness, or coma.*

The writer here quotes Bonfigli as follows:

"The patients when questioned appear not to comprehend the demand directed to them, and regard the interrogator with stuperous eyes until after having repeated the same demand a number of times there comes a brief response, oftentimes monosyllabic, but usually coherent."

Vedrani quotes Lombroso to the same effect, but as reference has already been made to that author's views on this subject their repetition is here unnecessary; mention is likewise made of the fact that Lombroso has observed in a few instances that the disease *actually exalts the mental faculties.* With the foregoing in view, Vedrani says that he cannot agree with Tanzi when that author remarks that "it is very rare when they can give any account of their past or know of their being in the asylum."

The writer agrees entirely with Pieraccini as regards the *hallucinations,* having observed them only in three instances, and in every case they had relation to water.

He observes that Finzi and Lombroso have both noted that patients *frequently repeat words or phrases without meaning or relationship to previous conversation;* this he has also observed. He notes a tendency in some patients *to make rhymes* and to *repeat phrase after phrase* where the words are in consonance; he gives several examples of this curious doggerel.

From the foregoing Vedrani strongly dissents from the view recently expressed by a prominent alienist (Finzi), who said that "he found no reason to give to the psychosis of pellagra a position apart in the classification of mental diseases, and no reason to exclude them from the category of confusional insanity."

The writer then takes exception to the conception of "amentia" (confusional insanity) as the word is understood by Meynert; very properly he joins Arndt in criticising this author's classification, who would make psychologic confusion the pathognomonic symptom in the diagnosis of a group of maladies which are fundamentally different. According to Meynert's view we should *differentiate mental diseases entirely by their symptoms,* but unfortunately it is true that where this is attempted we *include under the same head divers morbid conditions which differ in causation, course and termination.* Vedrani then would *strongly dissent from that conception of amentia* which particularly stresses mental confusion and illusions, but which cannot signify a morbid entity, and only indicates that the malady is of complex symptomatology.

As regards pellagrous insanity then this author says that the symptoms are so evident that we cannot fail to recognize them:—we have to do with a malady of an organic kind, quite as distinct as syphilis or alcoholism, in which there develops a series of harrowing symptoms the result of organic changes. We distinguish an *alteration of the gravest character in the disposition* in most cases, there being *anxiety* and *melancholy:* in some cases, however, there is *fairly constant euphoria* or an *opposite state of mind:* the patients present *delirious phases which change,* but which *agree harmoniously with the character of the humor;* in the less acute forms of the disease there is often *lucidity of ideas* and

orientation, and *memory is relatively conserved,* however much general appearances might lead us to a contrary conclusion; their own condition is recognized as in few other psychoses; *hallucinations are extremely rare,* and when they occur usually associate themselves with water; in many cases there is a tendency to *repetition of a clonico-anxious character of the same phrase,* and *logorrhoea,* with *association of assonance,* is continued with peculiar insistence; the *deportment is in conformity with the humor*—there being for the most part *restlessness;* lastly there is a *tendency to suicide.*

In the foregoing this author is quite conscious of the fact that he has simply collected together a description of certain symptoms, and he quotes Tanzi to the effect that data of this character are sterile without we at the same time study their origin. He recognizes therefore that such a description will not satisfy those who wish to probe the matter more deeply. Nevertheless he considers the catalogue of symptoms just recorded not to be without value, and calls attention to the fact that by careful observation alienists within recent years have distinctly separated mental diseases which had been previously regarded as identical. He says with truth that Tanzi is wrong in the view that it is easy to observe and describe the clinical manifestations of mental diseases, it being indeed a matter of extreme difficulty to do this correctly, and the ability to accomplish it he declares to be among the rarest of faculties.

Finally this writer says that we have in *pellagrous insanity a somato-psychosis, which as a rule slowly increases, but we are unable to say as to how far the mental symptoms are due to the direct action of the pellagrous poison on the cerebral cortex, and we are equally in ignorance as to the extent that the clinical picture is influenced by secondary alterations in the organs of the patient;* we do not know in what degree the clinical manifestations depend upon the excessive waste and insufficient nourishment of the nerve tissues in the cerebral cortex, and we are uncertain as to how far these results are occasioned by functional disturbances resulting from lesions of the digestive organs, the prolonged insomnia, and the frightful misery and actual hunger of which pellagrins are often the victims. We can only say—and in this there is no question that he is correct—that the *pellagrous poison has not a formidable potency, nor any tendency to attack quickly the psychic organs.* As proof of this he instances the well-known fact that in a great majority of cases the pellagrous psychoses only occur in old pellagrins. He is aware that Valtorta has stated that *pellagrous insanity may initiate an attack of pellagra,* and while agreeing that this is not impossible, he thinks it *unquestionably rare.* This author maintains strongly that in the beginning, and for a considerable period thereafter, the alterations in the emotional sphere are fundamental.

Vadrini maintains that it is not by any means always true, as stated by Tanzi, that the errors in judgment in true manic-depressive insanity are less grave and less constant than in the pellagrous psychoses simulating them; on the contrary he has observed that such patients do not show the slightest evidence of deliriant ideas. In other instances patients show permanent and constant alterations in the humor, which are dolorous, despairing, and anxious in character; on the other hand the *deliriant idea* is always fugutive and changeable, frequently recognized by the patient and cast aside, and is *invariably in conformity with the state of mind.* It therefore appears that in this malady the *deliriant idea is a secondary product, which changes and corresponds to the emotional state of the patient.* In this connection attention is called to the fact that Francois Franck *produced anxiety in animals by irritating the vagus,* and Lombroso has observed that the *organs principally attacked in pellagra are those supplied by this nerve.*

Originating in a different manner perhaps is the association of assonance, which was particularly marked in two cases. Aschaffenburg in his studies has always found that under the influence of weakness the number of the associations for assonance increases, while the internal association becomes less frequent; as proof he adduces the fact that logorrhoea in certain maladies comes on after severe hemorrhage, long continued insomnia, and from other influences that presumably weaken the patient. It is then thought by this author that similar conditions of exhaustion in pellagra probably explain the occurrence of these symptoms in this disease.

One of the most important of the modern articles on pellagrous psychoses is that of Gregor, whose observations were made in the province of Bukowina, Austria, and whose results are based on a careful analysis of the symptoms observed in 72 cases. This writer divides the pellagrous insanities into seven groups, which show the following peculiarities:

(1) The manifestations which these cases show are subjective, and consist of *headache, pain in the region of the stomach, a sense of pressure in the head, vertigo, depression, a feeling of restlessness and anxiety*, which increases to a *dread of some unknown calamity*, a *feeling of bodily* and *mental unfitness*, and a *sense of being ill*. The patients behave in a normal manner, and there is no serious mental disturbance, but notwithstanding this they are unfit for mental or physical activity. The *association of ideas is decidedly diminished*, the simplest question requiring long consideration before being replied to, the voice is low and anxious, and the hypochondriacal symptoms are increased by the subjective troubles, both on account of the knowledge that pellagra exists, and from the memory of severe illness in the past. In some cases there are *mild motor unrest* and *nervousness*, but *as a rule the patients appear to have slight motor insufficiency*, and in the end become resigned to a condition of idleness and apathy.

(2) The milder forms of this group merge into those of the preceding. The symptoms, there only suggested, are here openly manifested, and the *partial arrest of psycho-motor functions now increase to stupor*. The patients, who now give the impression of serious illness, lie for weeks *apathetic* and *without moving in their beds*, and *comprehend what is said to them only after many repetitions*. They *answer in only a few words*, or even *not at all*. The *simplest movements* are *slowly* and *painfully performed*, and often an *act begun is arrested in its earliest phase*, being forgotten after the idea has been grasped. As a rule it can be determined that the *patients preserve their orientation fairly well*, and one may recognize that after the arrest of psychic activity has occurred there are *momentary periods of intelligence;* only now and then at the height of the disease is the orientation disturbed; *illusions* occur, almost always the patient has a feeling of *insufficiency*, with now and then an *hypochondriacal* tendency, and a *recognition* of his *mental condition*. Patients react to the stupor depending upon the way that it develops. In a series of cases in which it came on gradually the arrest in psychic and motor activity occurred without marked disturbance. In other cases the perception of the rapidly approaching disturbance resulted in much mental perplexity. In the latter case the patients of their own volition seek a hospital after the disease has existed a few weeks, *because they recognize that they are no longer able to meet the demands of life*. Among such cases there are individuals who, as the progress of the disease shows, *have normally active minds*. Patients belonging to this class show a *marked loss of memory*,—this disturbance being particularly mentioned by Tanzi as characteristic of the affection. The writer says that he wishes particularly to combat the view of Warnock that weakness of memory is not a characteristic symptom of pellagrous dementia.

(3) This group, which is the most numerous of all, comprises those pellagrous psychoses which come within the category of *confusional insanity*. After a prodromal period, during which there occur the symptoms that characterize the first group, *horrible hallucinations supervene*, accompanied by *violent emotions* and marked motor excitability. The patient sees the house or a whole village in flames, enemies press upon him, he is attacked by animals, wolves creep under his bed, the devil appears, he is chopped into pieces or machines cut off his head; occasionally there are very horrible dreams, great throngs of ghosts come into view, or heaven itself opens, and priests, arch-bishops or God himself appears. These hallucinations *cause corresponding movements on the part of the patient*. He seeks to avoid the flames, attempts to defend himself, but not all of the movements appear to be connected with his hallucinations. The *duration* of this condition varies from a few hours to days. There then occurs a *greater or less interval*, during which the arrest of mental and physical powers continues, the patient being sometimes stuperous, but only shows slight disturbances of orientation, and he has a lively sense of the fact that he is ill; *following this another attack of dementia occurs*. The sense of orientation is sometimes lost in the periods between the attacks when these follow at short intervals.

A further series of cases show a *profound disturbance of consciousness,* the patients are *somnolent* and *talkative, delirium appears,* which cannot be differentiated from that observed in meningitis, typhoid, etc. The patients suffer particularly toward the end of life with profuse diarrhoeas, constituting what is known as typhoid pellagra. This condition develops either in such cases as have been described, or the mental disturbance comes on directly following the symptoms of intoxication and bodily weakness already referred to. Some of these *patients recover completely,* but *more commonly death ensues.* In some instances there is a *further stage of pellagrous insanity* characterized by a *high degree of dementia,* and the appearance of temporary states of *confusional insanity* (verwirrheitszustände), with now and then *hallucinations* leading to impulsive acts of violence.

The confusional state is not in all instances preceded by marked mental perturbation; under such circumstances there is usually a history of long-continued illness, with purely somatic symptoms, and only ephemeral outbreaks of hallucinatoins and insanity.

Finally there appear *katatonic symptoms* with *flexibilitas cerea, negativism, verbigeration,* and *stereotyped movements* and *attitudes* in some cases.

(4) The fourth group differentiates itself from the third by the greater *intensity of the mental aberration, hallucinations, dementia* and *motor excitability,* and a *rapid* and *fatal termination.* It would appear that the cases in this group might be properly called "acute delirium." It is remarkable, however, that there is *never an elevation of temperature,*—a fact to which various Italian authors have called attention, and which was the case in the three instances observed by this writer.

(5) This comprises a group of cases in which in symptomatology, progress and termination the *symptom-complex is that of katatonia.* The patients show no marked emotional disturbances. In one case there was *hallucinatory dementia,* while in three others the *psychosis terminated in simple dementia.* There was further observed *negativism, flexibilitas cerea, stereotyped movements* and *poses,* and *paranoiac symptoms.*

(6) One of his patients appeared to have a *fear psychosis,* as would be indicated by the *severe* and *fluctuating emotions of fear,* and *motor unrest* and *fear-delusions.* The patient complained of a pronounced feeling of insufficiency, and between the attacks was slightly *stuperous,* resembling in this particular cases in groups two and three. In another case at first *psychomotor arrest* accompanied by pronounced *emotions of fear* alternated with a lively *motor unrest.* In this case the patient had *delusions of being followed* and of having *committed sins;* here also a *stupor* finally supervened. The hallucinatory delirium in the first case would appear to show relationship to those in group No. 3. The third case showed the peculiarities of *typical depressive melancholia.*

(7) The patients in this group showed symptoms of *mania;* in one instance the mental state gradually change to that of *melancholia.*

It will be seen from the foregoing that this writer is a strong advocate of the *polymorphic character of the pellagrous psychoses.* Finally he summarizes his views on this subject as follows:

In pellagra mental disturbances occur which belong to various forms of mental disturbance. Of these groups 1, 2 and 3 belong in the category which, as respects development, symptomatology and progress, are *to be regarded as pellagrous in the strictest sense;* in other words these forms of mental alienation he regards as the direct result of the action of the pellagrous poison on the nervous system. It is likewise true that in the other forms of the pellagrous psychoses we have often throughout their course reminders of the fact that they are closely connected with pellagra.

The conception of a pellagrous *dementia* is justified by the facts; in the *terminal stages it may be differentiated* from the clinically closely related *dementia paralytica.* A more specific characterization of the milder cases is not possible; simple weakness of memory cannot, as assumed by Warnock, be regarded as a diagnostic sign of this condition. Where such a state is marked it can only be regarded as the expression of psychical arrest.

The study of a large number of cases made clear many of the contradictions which are present in the literature. The great variety in the symptoms observed explains the view that all forms of mental disturbances may occur in pellagra. On the other hand we are also able to understand the view that pellagra is *principally a melancholic psychosis,* since many cases with depressive symptoms and stupor have been seen. Gregor says that he is convinced with Finzi that pellagra as a rule is *not a true melancholia,* but at the same time *cannot agree that the depressed condition of pellagrins is the consequence of weakness,* as he has seen similar mental states in the well-nourished; likewise Warnock has known pellagrins to exhibit profound mental depression as the result of this disease, but at a later time show the typical manifestations of mania following a lowered state of vitality from other causes. The contradiction between the views of Finzi and Vedrani are explainable on the idea that they were not really considering similar cases; further, that hallucinations and disturbances of orientation only occur in pellagrous patients at intervals (zumeist episodisch).

Gregor would characterize the various groups into which he has divided the pellagrous psychoses as follows:

(1) Pellagrous neurasthenia. (2) Acute pellagrous dementia. (3) Pellagrous confusional insanity. (4) Acute pellagrous delirium. (5) Katatonic dementia. (6) A fear psychosis. (7) A condition resembling manic-depressive insanity.

Somewhat later Vedrani (2) replied to the criticisms of Gregor, and particularly called attention to the fact that this author acknowledged that "hallucinations and disturbances of orientation present themselves only now and then during the course of pellagrous insanity." And again, "In pellagra psychic disturbances arise which appertain to the most diverse forms of the psychoses."

Vedrani then justly says that he was quite correct, according to Gregor himself, in opposing the view that the *psychopathies of pellagra belong purely and specifically to the type of confusional insanity.* The writer says, even as acknowledged by Gregor, he has combatted for three years the tendency to baptise with a name and to include forcibly within the narrow confines of a single formula the great variety of psychic symptoms that occur in pellagra.

Vedrani again here quotes the words of Tanzi to the effect that the pellagrous psychoses, while presenting the appearances of melancholia, are in reality typical of what is called amentia,—a view to which this author makes strong objection. The truth is, he says, that the pellagrous poison, *like other psychopathic agencies* (such as that of manic-depressive insanity, progressive paralysis, epilepsy, etc.), not only has the power to develop the syndrome which Meynert observed in epileptics and alcoholics, etc., and called by him amentia (confusional insanity), but it can also under certain conditions produce symptoms of melancholia; the last named condition has as its nucleus mental depression, which, added or not to other symptoms, takes various forms in various maladies and in different cases in the same disease, and exhibits varying phases in an individual case.

Perhaps the idea that confusional insanity is the peculiar psychosis of pellagra has insinuated itself into the thoughts of the writers just quoted, without really verifying the facts, by a deduction from the conception, largely diffused, according to which "beyond doubt the clinical type most frequent in the toxic psychoses is that of mental confusion."

Vedrani says that to this there are many exceptions; it being true, for example, that in both acute and chronic alcoholism there is a much nearer approach to hypomania than to mental confusion; likewise that the first affect of cocaine is excitative, with greater capacity for action and greater force, and that even in the insanities from this drug the consciousness of the invalid is always so clear that they not only talk properly, but have the capacity to give in a coherent manner information concerning their condition. Morphine likewise produces an increase in excitation of the intellectual faculties—the opposite of mental confusion. It is therefore seen that confusion is not an essential element in psychic disturbances the result of toxic action, though the general acceptation of this opinion has doubtless influenced many writers on this subject to conclude, *a priori,* that, since pellagra is undoubtedly the consequence of an intoxication, the mental symptoms must be those of amentia.

He quotes Gregor to the effect that the patients included within his third group show the following traits:

"Short, furious delirium, anxious behavior, frightful delusions, in which fear plays a frequent part, states of stupor of greater or less duration, and an *intense sense of illness.*"

Not alone then says Vedrani in the other groups, but in the particular one characterized by wandering of consciousness, it is specifically admitted that the patient's mentality is preserved at least to the extent of knowing that he is very ill.

This author admits that at certain phases of its variable course the pellagrous psychoses may take on the characteristics of amentia. It remains however to be seen if the apparent eclipse of consciousness and disorientation are not the result of superficial exploration much more commonly than is generally admitted; there are indeed in this disease moments of hallucination in which the individual is simply distracted on account of the apparitions which appear to him, and there are tetanoid, terminal states in which external appearances of confusion occur, but on close inspection it will be found that the sufferer has not lost all consciousness, either as regards his personality or his disease, and if the observer insists on inquiring the patient will overcome the impediments and show that his lucidity does not sleep even in the struggle of the ultimate hour.

More recently Ziveri has written a very complete and full article on this subject. His conclusions may be summed up as follows:

"Under the head of pellagra one can understand a clinical picture that is not simple, since there may be a number of different manifestations which when taken together show that there are two forms of the trouble; the one causes a *pronounced change in character,* with *incomplete* and *varying orientation,* which, in some cases, takes on a *febrile* and *severe type,* with *marked bodily manifestations* (accompanied possibly by an affection of the intestinal tract); and another form of a *depressive, anxious character,* with *slight indications of delirium* and *delusions,* along with *insight into the character of the disease,* and a *well maintained power of orientation.*"

The author does not believe that we are able to differentiate the fluctuations in orientation and lucidity common to toxic and confusional insanities with that degree of clearness which, according to Vedrani, can be done in the pellagrous insanities, nor does he agree with Gregor in the conception which necessarily connects them with the well recognized, classic mental disturbances.

Another very intelligent writer on this subject is Valtorta (4), who criticises very justly the character of our literature on the pellagrous psychopthies; he refers to "insane pellagrins," and "insanity in pellagrins," which are so often confused with mental alienation the result of pellagra, and agrees with Finzi that there is a great disposition in those countries where pellagra is common to regard all forms of mental aberration as being the result of this malady. He says:

"It is not possible to include the various consequences of maize poisoning in a fixed succession or definite stages, but we must recognize that certain manifestations make their appearance when *pathologic alteration* has already occurred, while on the other hand other symptoms develop during the stage when the *disease is still a toxaemia.* The inherent peculiarities of the malady are such that no such thing as a typical and constant form is possible, either as regards its beginning, the physiognomy of its clinical manifestations, its course, or its termination."

According to this author's views the maize poison united with the tissues of the body acts upon them in various ways until they are neutralized or eliminated. The crepuscular premonitory scene is clinically manifested by *disordered functions,* which is *periodic,* and is most responsive to a proper therapy. The poison does not have a tendency to produce at once marked symptoms, it being in a sense nursed within the organism. It slowly and gradually undermines the organs that are weak, and ultimately gives rise to a clinical picture which is the *result of all the alterations which the toxine may have produced.* Those organs which are most used are naturally those which are most affected.

The writer closes his article with the following conclusions:

(1) The prodromic symptoms, along with the altered functionating which ushers in the pellagrous state in an organism properly prepared, may become aggravated in a primitive and autonomous manner, and thus give color to the clinico-psychic picture before other manifestations of the malady may be objectively discernible.

(2) If the phenomena of mental disturbance come on during the chronic stage of the disease they take on the characteristics of the psychopathic states which have an anatomical basis in cerebral involution and alteration.

(3) Alcohol accelerates the development of pellagra; it may immediately give rise to symptoms of a psychosis where given to a patient with advanced pellagra, playing the part of a simple secondary morbific element. If the two conditions accompany each other from the beginning the clinical picture is complex, a double set of phenomena being developed. The characteristics of the physical symptoms, and above all the inherent method of their expression during the course of the psychopathic manifestations, must be our guides in differentiating.

"The maize toxine saturates the body in a slow and progressive manner, and is the cause primarily and immediately of psychopathic phenomena."

"The pellagrous psychosis is a *classical toxic mental* state." * * * * *

(4) The *pellagrous virus would appear to have an action analogous to that which would result from an incomplete psycho-evolution*, particularly if complicated by dystrophism, as, for example, that caused by altered thyroids.

Rezza has recently written a critical essay on the various modern works on the pellagra psychopathies. He is not inclined to agree with the classification of Ziveri, and expresses some doubt as to the correctness of Valtorta's conclusions, inasmuch as some of his cases had suffered from chronic alcoholism, some with malaria, and some with congestion of the brain which had lasted a long time.

Still more recently Pearson has written an interesting article on the pellagrous psychopathies as they occur in Egypt. Respecting the mental symptoms he says:

"The mental symptoms are usually of the *melancholic type*, but there are occasionally cases of *mania* which sometimes become furious." * * * * *

"We have also two mental cases at present who on admission were typical pellagrins, having the usual rash and other symptoms. After some months residence in the asylum the skin peeled off, and these patients, *to all appearances, became typical general paralytics*, with slurring speech, Argyll-Robertson pupils, tremulousness of the tongue and facial muscles, markedly exaggerated knee-jerks, and incontinence of faeces and urine. Both of these cases are young men not over thirty years of age, and so far as can be observed clinically they have no sign of congenital or acquired syphilis. No symptoms of general paralysis were apparent on admission."

As a rule alienists have not tried to distinguish between the *insanities presented by hereditary and acquired pellagra*, but this has been attempted by Agostini (7). He divides the former into two classes:

(1) Those that present *grave symptoms of physical degeneration*, with *congenital mental defects* varying from *idiotism* to *complete imbecility;* in other cases there is *simply mental weakness, sometimes associated with epilepsy, chorea, hysteria*, and *neurasthenia.*

(2) A milder form *characterized by a simple melancholy* and *mental confusion;* with this there is associated *hypochondria* and *various nervous disturbances.* Less frequently there is *stuporous dementia*, with *hallucinations*, or an *anxious melancholy* with *delusions of persecution* or of *being damned.* Many patients present a simple *benumbing* and *weakening of the intellect* of the kind which terminates in *tranquil dementia*, with symptoms suggesting *disturbances of the spinal nervous system*, and of the *sympathetic ganglia.* More rarely there is *manical excitement*, and still more infreqsently *symptoms of general paralysis.*

Still more recently this subject has been again investigated by Valtorta (3), he having made observations on 18 hereditary pellagrins who presented symptoms of mental alienation. The writer correctly says that *it is impossible to say how far the mental changes are to be ascribed to hereditary influences and how far those that are acquired.* In three of his cases the patients were in the last

stages of pellagra, and presented a condition of *dementia* which had been *preceded by hallucinations* and *confusion*. In three others there were *symptoms of manic-depressive insanity*. The remaining cases the author made no attempt to classify.

More recently Gatti (3) has maintained that, while individuals would frequently pass through life perfectly sane were it not for the pellagrous poison, it is nevertheless true that there is no such thing as an insanity due to this cause alone; the poison simply lights up the process, which, fundamentally due to other causes, previously lay dormant. The psychic disturbances are polymorphic: there are confusional insanity, a state of mental depression, the alienation that occurs in typhoid pellagra, and dementia; of those the second is the most characteristic, and comes nearest being a true pellagrous process.

Nymphomania is said to occur only rarely.

So far comparatively little attention has been given to the pellagrous psychoses in the United States, though recently several excellent papers have been written on this subject.

The first of these was an article by Mobley, written in 1909. It is particularly interesting to note that this paper contained the first attempt at classification of the abnormal mental states encountered in pellagra that appeared in English, and that the only other writer along similar lines who preceded him was the German Gregor, whose monograph was published in 1907.

Mobley's classification is as follows:

First.—"The cases showing a profound intoxication, with early delirium, high temperature range, with symptoms pointing to acute organic changes in the cord or brain.

"Controlling phase: Complete or incomplete psycho-motor suspension.

"Classification: Acute Intoxication Psychosis.

Second.—"Those cases of an apparent mild infection with some mental anxiety, apprehensive hallucinosis, gradually increasing mental confusion,—finally delirium,—temperature subnormal or slightly elevated,—this type usually covering six weeks to two months or more, ending in a slow but progressive exhaustion.

"Controlling phase: Psycho-motor Retardation—Excitation (active, passive).

"Classification: Infective Exhaustive Psychosis.

Third.—"Those cases showing symptoms of mild melancholia, chronic in character, with remissions and exacerbations, impending fear, suicidal tendency, due more to apprehension than self-reproach; temporary recovery.

"Controlling phase: Psychomotor Retardation (inconstant, passive).

"Classification: Symptomatic Melancholia.

Fourth.—"Those cases of mixed type showing at times symptoms of depression, exaltation. confusion, impulsive acts, apprehensive hallucinosis, exhaustion, slow mental reduction—including the Dementia Praecox Class.

"Controlling phase: Psycho-motor Retardation—Excitation (Active, passive, negative).

"Classification: Manic-depressive—allied states.

Some years later an interesting statistical article was written on this subject by Green, who published the results of his findings in 131 cases, to which Dr. Green, in a personal communication to the author, kindly added his notes on 20 other cases, there thus being 151 cases in all.

As regards *race* and *sex* there were 40 white males and 16 colored males, and 47 white females and 53 colored females.

Of this number 95 were married, 27 were single, 17 were widowed, 10 divorced, and in 2 cases no information bearing on this point could be obtained.

As regards *occupation* 78 were farmers, 31 were domestics, 20 were mechanics, 12 were tradesmen, 4 were professional men, 2 claimed no occupation, and in 4 instances the former pursuits were unknown.

The average *age* was 37 years, the youngest being 16 and the oldest 69. There were 19 from 20 to 25, 21 from 25 to 30, 26 from 30 to 35, 17 from 35 to 40, 13 from 40 to 45, 17 from 45 to 50, 10 from 50 to 55, 9 from 55 to 60, and 13 over 60.

Of the 20 cases personally reported to the author by Dr. Green 12 were from the country, 7 from towns and cities, and 1 unknown.

As regards their *previous circumstances*, 35 had formerly lived in poverty, 72 in comfort, 25 in affluence, and no data were obtainable in 18.

The average *duration* of the insanity was in the neighborhood of 6 months, the shortest being 7 days and the longest 8 years.

The psychoses were *classified* as follows: infective exhaustive 79, manic-depressive 19, dementia praecox 16, paresis 6, melancholia 3, undetermined 27, paranoiac 1.

The following *complaints were noted*: headache, vertigo, weakness, pain, formication, numbness, nervousness, and precordial distress.

In some cases *impairment* of *special senses* was complained of, there being disturbances of vision in 8 cases, of hearing in 17, of smell in 33, and of taste in 15.

Alterations in sensation were occasionally noted, being in some cases increased and in others diminished.

The *reflexes* showed marked alterations, myotatic irritability being increased in 160 instances, diminished in 10, and absent in 3; the superficial reflexes were increased in 13 instances, diminished in 5, and absent in 6.

Romberg's sign was noted in 24 cases, while the *Babinski reflex* was observed on both sides in 6 instances and on one side in still another.

Tremor was noted in 105 cases.

Pronounced *disturbances of emotion* were noted, there being in 5 suspicion, in 62 depression, in 19 exaltation, in 25 apathy, in 22 irritability, in 21 excitement, in 62 apprehensiveness, and in 4 confusion.

Disturbances of thought were frequent, there being in 29 cases retardation, in 9 flight of ideas, in 6 distractibility, in 22 incoherence, in 9 irrelevance, in 45 confusion, in 14 unproductiveness, and in 5 change of personality.

There was *disturbance of will* in many cases; 53 showed restlessness, 23 violence, 17 destructiveness, 28 negativism, 3 sphincter weakness, 2 slowness of motion, 1 refusal of food, 13 mutism, 8 catalepsy, 9 stereotypy, and 6 impulsive acts.

Many patients showed *disorientation;* 4 for place, 15 for time, 1 for person, 6 for time and place, 3 for time and person, 2 for place and person, and 68 for time, place and person.

Impairment of memory was shown in 24 for recent events, in 11 for remote events, and in 62 for recent and remote events.

Retention was impaired in 78 cases and lost in 31.

Attention was impaired in 54 and lost in 9.

Grasp of school knowledge and general information impaired in 50, and much impaired in 36 cases.

Counting was impaired in 38 and lost in 11 cases.

Calculation was impaired in 50 cases and lost in 23.

Insight was partially preserved in 47 cases and lost in 70.

Judgment was impaired in 50 cases and much impaired in 74.

Hallucinations were not uncommon; 11 were visual, 34 were auditory, and 55 visual and auditory.

Delusions were not uncommon; they were in 7 cases expansive, in 29 depressive, in 61 persecutory, in 3 somatic, in 10 of influence, and in 8 character not stated.

Of *miscellaneous* there were in 3 cases stupor, in 17 volubility, in 21 boisterousness, in 9 mumbling, in 27 suicidal tendences, and in 24 inaccessibility.

It is interesting to observe that the *duration* in these cases was well beyond twice as great as is the case in the old world. Whether this be due to increased severity in America or to mistakes in diagnosis it is at present impossible to say. It is greatly to be desired that some one should collect and publish statistics where the patients' antecedents could be definitely determined, as only in this way will it be possible for us to arrive at an accurate idea as to the characteristics of the pellagrous psychoses in our country.

Quite recently Singer has published an interesting paper on the pellagrous mental disorders, and has likewise proposed a new classification, which now follows.

I. Disorders directly due to pellagra toxine (or toxines).

(1) Symptomatic depressions.

(2) Delirious pictures.

II. Disorders based on peculiarities and personal make-up, "the attack of insanity being precipitated by pellagra."

(1) Manic-depressive disorders.

(2) Hysteria.

(3) Psychasthenia.

(4) Dementia praecox.

(5) Paranoiac developments.

III. Disorders due to definite brain changes, with pellagra merely as a complication.

(1) Arterio-sclerotic dementia.

(2) Senile dementia.

(3) Pre-senile sinuses.

(4) General paralysis of the insane.

The disorders in Group I. he considers in detail, while the others are passed over more briefly.

Symptomatic depression. This is the most common of the types, and corresponds to what Gregor called the neurasthenic type. The main characteristic of them is that the *attitude of depression runs parallel with the other manifestations of pellagra, improving as they improve and becoming worse as these other symptoms become more severe.* The picture presented is that of a more or less *hopeless sadness,* with all that this implies in regard to the activities of the body as a whole. There is a *general lowering of tone and energy, thinking* and *attention are more or less difficult,* and *activities are diminished.* Obviously the exact mode of expression will vary with the personality of the patient, just as the words he uses to indicate his feelings depend on his personal experience and habits of adjustment.

Delirious pictures. This is characterized by a *clouding* of *consciousness,* together with *sense-falsification,* especially of illusory character; the *reactions* of the patient in *word* and *act being conditioned by this dream-like state.* The vast majority of such condition pictures are the result of intoxication of the brain, with consequent general lowering of functional activity, which involves first and most the highest cerebral levels. All degrees are met with in pellagra. In mild forms the *clouding may be brief and episodic,* and during the *intervals there is symptomatic depression.* Periods of *delirium* recur from time to time in some cases.

(2) About 95% of the mental disorders are the direct result of the pellagrous intoxication, and although the mortality in such cases is much higher than

in those without such disorder, yet the mental disturbance will fully subside if the patient survives. Such changes correspond to similar disturbances in other somatic diseases, and in such cases are often not regarded as insanity. The remaining 5% are examples of mental disorder primarily dependent on the individual's make-up, or else are merely concomitant. As an explanation of the frequence of insanity in pellagra, the author thinks that *faulty nervous organisation plays an important part.* Apparently he fails to recognize the fact, particularly emphasized by Valtorta, that congenital defects of the central nervous system in pellagrins are but too often the consequence of a pellagrous ancestry.

(3) Chronic insanity, due strictly to pellagrous intoxication, if it occurs, is rare and the same may be said of chronic nervous disease.

Unfortunately that great American pellagrologist Babcock, seems nowhere to have written extensively on this phase of the pellagra problem, though his views appear to be briefly expressed in the following: He says, "Mental symptoms usually assume the type of melancholia. The milder forms show merely a retardation of ideas, disinclination for thought and activity or simple mental depression. Later, the disease may advance to a profound melancholia, even refusal of food, and suicidal tendencies manifesting themselves. Maniacal symptoms are rarer, but sudden outbursts of delirium or excitement may occur in cases of apparent stupor." (3, p. 708).

In addition to the typical forms of the pellagrous psychoses described in the preceding pages, there not uncommonly deevlops in pellagrins, particularly in the last stages of the disease, a condition of intoxication, which on account of its resemblance to the fever of that name has been called "typhoid pellagra," and in which there always occurs a state of *acute delirium,* which should evidently be looked upon as *quite different from the more typical mental manifestations,* and which is undoubtedly largely the *result of an acute process, probably of infectious character.*

From the foregoing rèsumè of the mental symptoms that occur in pellagrous insanities it will be seen that there is a wide diversity of opinion as to their true characteristics. On superifical examination the observer is struck at once on being brought in contact with those suffering from pellagrous psychopathies, by their mournful countenance and general air of profound dejection, from which it seems impossible to arouse them. For hours and even days they sit in retired corners or lie in bed, scarcely ever speaking and never doing so without being aroused. Though limited to comparatively few cases, it has been the author's uniform experience that on being urged to reply to a question frequently repeated they will ultimately give a rational answer, though the first reply may be irrelevant and apparently indicating that the patient has not been able to bring to bear his reasoning faculties in such a way as to speak intelligently. There would thus appear to be a condition of intellectual slowness, probably resulting from a state of weakness of the brain analogous to that observed in the body. As the patient grows worse his gloom deepens and the readiness with which he replies to questions gradually grows less and less until ultimately he sinks into a condition of profound delirium, which ends in stupor before death. The author has never been able to convince himself with Vedrani that even to the end these patients preserve in a measure their intellectual power, but he agrees with him fully that in typical uncomplicatd cases of undoubted pellagrous insanity the mental faculties are astonishingly well conserved, even to a very late stage of the disease. He has frequently carried on conversations in the presence of a pellagrin, who was apparently entirely insensible, and has been informed by the nurse, or by some member of the family at a later time, that the patient had afterwards referred to the matter discussed in such a way as to show a remarkably clear conception of what had been said.

As to whether or not confusional insanity is to be regarded as a common form of mental alienation in pellagrins it is difficult to say with certainty. As already pointed out, the distinguished Italian alienists Finzi and Tanzi hold that it is characteristics of all pellagrous insanities, while Gregor, who carried on his investigations in Austria, admits that the great majority of these cases presented this psychosis in a typical form; certainly a casual examination of these patients would lead one to this opinion in the great majority of instances, but the author

is inclined to think that a more careful study of these cases will show that the view is erroneous. It is clear that the final decision as to the true character of the pellagrous psychopathies can only be made after this subject has been further studied by other competent investigators.

As to whether or not true forms of manic-depressive insanity occur is likewise a matter of doubt, but that the clinical phenomena often closely simulate this condition there can be no question,—not only as regards the general symptoms the patient presents, but in the characteristic preservation of the mental faculties. It is likewise unquestionably true that these patients occasionally exhibit symptoms closely resembling those that occur in general paralysis, though in such instances it would be extremely difficult to exclude definitely the common etiologic factor in the production of this malady.

Unquestionably a great source of error in this connection is the tendency of many writers on this subject to regard as pellagrous all insane persons presenting any of the other classical symptoms of this malady,—an error which certainly most frequently occurs—and one which results in the greatest confusion. Under such circumstances it is quite possible for mistakes to be made of two quite separate and distinct kinds; in the one case the mental symptoms may well be the result of some other cause, even in pellagrins, and in the other, which is doubtless still more common, mental alienation in non-pellagrous individuals may be mistaken, particularly in its latter stages, for this disease. It is not unlikely that the apparent instances of typical circular insanity that have been unquestionably observed in pellagrins are then, in reality, the consequence either of an inherited or acquired tendency to this disease, to which the pellagra may well play the part of a secondary exciting cause, and that the apparent cases of general paralysis are to be accounted for in a similar manner. On the other hand there can be no question, in the author's opinion, of the extreme frequency of the mistake of regarding as pellagrous all of those cases of insanity where the patient develops diarrhoea or shows the slightest evidence of chronic skin changes; errors of this character have undoubtedly very commonly occurred in institutions for the insane, and probably make up a not inconsiderable proportion of the cases of alleged pellagra that are at the present time being so freely diagnosticated in sanatoria for the mentally feeble throughout our northern states. It has long been known that erythemas on the extremities and cachectic diarrhoea are extremely common in the later periods of depressive insanity, of dementia, of progressive paralysis, and of lipemanic stupidity, as pointed out over a half century ago by the committee headed by Tardieu, which was appointed by the Society of Hygiene of Paris to investigate this question. As improbable as it would seem, there are even many instances on record where pellagra has been reported in the insane where the diagnosis was made from skin lesions which were later shown to be simply ringworm. The author then strongly feels that we should accept with extreme caution reports of cases of pellagra emanating from sanatoria for the insane in districts where maize is not eaten to any great extent, and particularly where the presence of pellagra is not confirmed in the neighboring districts by the presence of this disease, unaccompanied by pronounced mental change.

In conclusion attention should be called to the very pronounced alterations that occur in the brain substance in pellagra,—alterations that unquestionably have a great deal to do with the production of the mental symptoms. Indeed the author questions as to whether it is ever the case that the psychopathies occur preceding the development of these changes, and it seems not unlikely that they are at least the determining factor, if not the sole causative agency, in the production of the mental symptoms that occur in this disease.

According to Tanzi, about 4% of all pellagrins develop a sufficient degree of mental alienation to require special treatment in sanatoria for the insane.

Tuczek says that on the whole about 10% of pellagrins become mad in Italy; in some places, as in Lombardy, it is said that the proportion is higher, being about 15%, and in Venezia 35%.

Singer says that mental disturbances occur in about 40% of all cases in America; children are practically exempt.

MEDICO-LEGAL.

The medico-legal aspect of pellagra has in the past by no means received the attention which it deserves,—having been apparently crowded out of consideration by the array of more vital and insistent problems with which this subject bristles. Indeed, it may almost be said to have been ignored, for, with the exception of the admirable article by Babcock—presently to be considered in detail—it cannot be said that any writer has given the matter more than casual attention.

When it is remembered that the unhappy victims of this affection are plagued with a multitude of both physical and mental ailments, of a most intractable character, persisting usually through a period of many years, and naturally giving rise to profound mental depression and melancholy, it is not to be wondered at that they are often driven to *acts of violence*, leading to *destruction of property, injuries to themselves* and *those with whom they come in contact*, and not uncommonly to *suicide or homicide*.

Zanetti appears to have been the first writer to have distinctly called attention to acts of this kind by pellagrins, he having observed that where they do not die from other causes they not infrequently drown themselves (* * * quod sequitur mors, nisi hanc ante incurrerint se sponte aquis submergentes, ut saepe accidit, p. 120). So common did the great Strambia find this tendency in pellagrins that he dignified it with a special name,—*hydromania*, (p. 17). Soler mentions a case where a woman committed suicide by throwing herself from a window, and was himself a witness of attempted self-destruction by another female pellagrin, who, being left alone for a short time in a house, constructed a sort of a funeral pile of some of the furniture, and, after getting it to burning properly, threw herself into the "living flames;" fortunately at this moment a domestic happened to return, and rescued the unhappy victim, but only after a severe struggle, (p. 14). Soler observes that in his experience cases of this kind are almost exclusively confined to the female sex. G. Frank (1) mentions a case where a pellagrin amputated his genital organs with a knife. Somewhat later Brierre de Boismont, in his extended studies of the pellagrous insanities, pointedly called attention to the frequency in pellagrins of suicide by drowning, and noted the fact that women suffering from this disease were not uncommonly obsessed with the idea of killing their offspring either by drowning or strangulation.

The foregoing observations were without exception made in the course of general discussions respecting the symptomatology of pellagra, there having been in none of the earlier writings on this subject any attempt to take up and examine the medico-legal aspects of the problem. In the years that followed more or less isolated references to the subject are found in the works of several pellagrologists, without anything new being added, and no one appears to have assayed a separate consideration of the matter until Landouzy (1) devoted to it a short chapter in his book on "Sporadic Pellagra," published in 1860. It is true that Sorbets, in the article presently to be again mentioned, says that he submitted a monograph on pellagra in 1859, which contained a full discussion of its medico-legal aspects, to the Academy of Medicine in a contest for the Barbier prize, but the author has been unable to find any evidence of its publication.

In 1862 Bouchard (1) devoted a short chapter to this subject in his well-known book on pellagra, but brought out nothing new.

In the same year du Saulle wrote what is undoubtedly one of the most important papers on this subject which has so far appeared; he mentions that in some cases of pellagra there develops, and sometimes persists for a long time, a *suicidal* and *homicidal* tendency, which should never be forgotten in connection with the medico-legal relations of this affection; of still greater interest and importance are those instances—referred to in this monograph in the chapter on the psychoses of pellagra—where *mental aberration occurs before any of the other characteristic symptoms appear*,—particularly where the subject resides in a district where this malady is uncommon; he justly concludes that where it can be established that mental disturbances have developed in a pellagrin his irresponsibility should be recognized by the courts in all civil or criminal actions.

Three years later Billod (2), in his bulky volume on pellagra of the insane, gives his views on the medico-legal aspects of this affection in a special chapter, but it contains nothing of importance and certainly nothing new.

In the same year Sorbets wrote a paper on this subject, in which attention is again called to the fact that *crimes of various kinds* may be committed by insane pellagrins, and for which they clearly cannot be considered responsible.

Tamburini (2) has recorded a case of *cleptomania* which was supposed to have been of pellagrous origin.

In the last edition of his well-known work on pellagra, published in 1892, Lombroso, while making no attempt to consider the subject in a systematic manner, still discusses some of the medico-legal relations of this disease; he especially calls attention to the frequency of *suicide by drowning,* and gives much curious and interesting information respecting the reasons therefor, with many illustrative cases. He says that in some instances there appears to be an actual passion for water, probably sometimes induced by the intolerable burnings so common in pellagra; also, when moving, water has a lively, sparkling, and inviting appearance, giving back the image of the beholder, suggesting that within its cool depths he will find peace; this, in its effects on the mind, perhaps resembles the impression produced on some pellagrins by a bright fire, which is known to be attractive to them. In other cases the subjects have as a great dislike for water —even amounting to horror—but nevertheless they are drawn to it much as some persons have an almost irresistible impulse to jump from heights. In other cases the subject seems to be impelled by a sort of blind, unreasoning influence resembling automatism. Some pellagrins find it difficult or impossible to perform certain acts, such as defecation or urination, without being more or less immersed in water, and under such circumstances vertigo may develop to a degree that drowning may result. Others seem to obey suggestion, resulting in their throwing themselves into water, implanted in the mind while under the influence of pleasurable hydromaniacal states. In some instances suicide of pellagrins by drowning is the result of illusory commands received while in a state of mental obfuscation, telling the unfortunate victim that he is condemned to drown, that if he does not drown himself he will be damned, or he hears a voice say "drown;" in some rare instances a mother has been known to cast herself into a lake to search for her child. Lastly, driven to suicide by their sufferings, some pellagrins deliberately choose drowning. This wirter tells of an interesting case of a woman who informed the authorities that she had been assaulted, and had subsequently given birth to a child which was buried alive; for months she led the police from place to place in an endeavor to find the body, until, becoming suspicious, they had her examined by a physician, who found that she was a virgin, and a pellagrin.

This author finally concludes that *vagaries of memory, self-accusations, nosophobia, loss of personality, concealment of sex, apprehensions of personal violence,* and *delusions of pregnacy* all have been observed in this disease.

Alpago-Novello (5) records *infanticide, suicide* and *homicide* as among the crimes he has observed in pellagrins.

Babcock quotes Antonini as saying: "In pellagrous regions there are frequent cases in which it is possible to find in indicted persons some outward expression of pellagra, even when the examination is made some time after the actual deed or during the progress of the trial. * * * To the expert alienist it will not be difficult to establish his case in persons sufferings from severe pellagra. Usually these facts will have been recorded by the examining physician who has sent the patient to an insane asylum. But pellagra may be present in an able-bodied farmer who has not felt the need of medical advice." The foregoing statement is of great importance, correctly pointing out the possibility of *apparently healthy persons committing crimes of various kinds for which they cannot be rightly regarded responsible,* according to the accepted views as to culpability, for the reason that they are not mentally sound.

In his work on mental diseases, Mongeri has somewhat discussed the medico-legal aspects of pellagra, but, like so many others, has failed to realize the almost boundless possibilities of this protean malady. While admitting that in externally well-developed cases—meaning by this those who already exhibit the skin changes

and other physical phenomena which characterizes this affection—such a state of mental unsoundness may exist as would easily warrant the conclusion that the subject is not responsible for his acts, he holds that in the earlier stages, before such symptoms have long persisted and become pronounced, no such attitude on the part of the courts would be justified. Than such a view nothing could be more incorrect. If the clinical history of this disease teaches us anything it is that we can never count on the different symptoms developing themselves in any regular order,—some of the worst cases of insanity coming on before there is the slightest evidence of any of the other marked clinical manifestations.

Warnock (2), who made his observations in Egypt, refers to the frequency with which pellagrins *commit murder,* and says that they are prone to *suicide,* and to *injure their children.*

Sandwith (2), who also made his observations in Egypt, in discussing the mental aspects of this malady, says: "Many criminal lunatics brought to the Cairo asylum are found to be pellagrous, they have been arrested for some purposeless murder in consequence of delusions which they forget and deny a few days after admission. One such case was said by his family to be quiet generally but to have violent outbreaks every winter. He remained melancholic but quiet at the asylum for eleven months and then suddenly (in Jan. 1904) attacked another patient without warning, and would have killed him if the attendants had not interfered; his excuse was that the man was beginning to persecute him." (p. 302).

So far as the author has been able to find American writers have given the medico-legal relations of pellagra but little consideration, although what has been written is of much interest and importance.

In this connection Saunders (1), in a paper devoted in the main to other aspects of the pellagra problem, has mentioned two very interesting cases in which the patients, after having what appeared to be typical labor pains, were *under the delusion that they had given birth to children.* In one instance the patient *insisted for weeks that a child had been born,* expressed great anxiety as to its wellfare, and accused the physicians of cruelty in removing and concealing it from her.

So far as the author has been able to find Babcock (6) is the only American author who has written an article on this phase of pellagra, and his paper therefore takes rank as the one important expression of opinion on the medico-legal relations of pellagra in this country, and is moreover easily the best publication on the subject in any language. The author feels that all students of the disease owe this writer a debt of gratitude for pointing out the importance of the matter, as well as their thanks for the interesting data which he has so carefully and painstakingly collected; in addition the author wishes especially to acknowledge his indebtedness for several references which had before entirely escapes his notice. Unfortunately space forbids more than a summary of this important communication. The data collected by Babcock—which will now be briefly considered—were all obtained in this country,—the states concerned being North Carolina, South Carolina, Georgia, Tennessee, Alabama, Mississippi, Louisiana and Texas.

There was one case of *murder,* the perpetrator having been acquitted on account of pellagrous insanity. He mentions another case where a woman *attempted to kill her children.*

He obtained data concerning 19 instances of *suicide,*—12 females and 7 males.

Of the former 6 accomplished the act by drowning, 3 by hanging (one a negress), 1 by poison, 1 by stabbing herself with a knife, and in another case the nature of the means employed was not stated.

In the case of the males 2 employed poison, 1 drowning, 2 shot themselves, 1 threw himself under a moving train, and one, who was a negro, beat his brains out against a house.

In 5 cases females attempted suicide, but did not succeed; of these 2 cut their throats with a knife, another tried to commit the act both by drowning herself and by inhaling gas, still another employed drowning and poison, and the last tried to jump from a window.

This writer relates an interesting case in which an insane pellagrin suddenly *bit off the tip of his tongue,* and the *end of a finger,* and *tore out the nails* from two other fingers; when asked why he did the act he replied, "I did it because I could not help it."

Babcock also speaks of a woman who on 6 or 7 occasions sent for her physician with the idea that she was *about to be confined,* alleging that she had *labor pains,* and asking to be relieved.

This writer also speaks of a case where *suit was entered by* certain persons with the object of *breaking a contract,* giving as the grounds that one of the parties had pellagra, and was of unsound mind.

Babcock quotes Watson, of Columbia, S. C., as saying that probably 90% of pellagrins are given to *uttering untruths,* and makes the interesting suggestion that this disease may be one of the causes of *pathologic lying*—technically called "pseudologia phantastica."

From the foregoing it will be seen that here in America, as in Europe, pellagra has a very important medico-legal aspect, and that it deserves the most careful consideration of all who have any interest in or connection with forensic medicine. Certainly in all legal actions—whether civil or criminal—where it is suspected that any of the parties concerned are victims of this malady it behooves those who are responsible to make a most careful inquiry, and if possible determine whether such persons are mentally competent.

Diagnosis:—It would not appear that it is here either necessary or advisable to indulge in a lengthy discussion as to making a diagnosis in cases of this kind. The insanities that are so common in pellagrins depart in no very special or essential particulars from those that are observed in persons not the subjects of this affection,—with only the not-very-important difference that in the former there is a marked and very peculiar tendency to drowning. On the physical side we are aided by the fact that in no other forms of mental alienation does the subject exhibit anything like the same number of well-marked symptoms as in this disease,—symptoms which alone in most cases easily establish the character of the trouble, and point the way to the medical expert. He should never forget, however, that in some of the worst cases the mental phenomena precede all of the other symptoms of a marked or characteristic nature. Naturally the diagnosis will here rest on the same clinical signs and symptoms which guide us in investigations undertaken to determine the presence of this affection under ordinary circumstances, and to the chapters where these are considered the reader is referred who wishes further information.

TYPHOID PELLAGRA.

For almost a century we find in papers dealing with this disease frequent references to "*typhoid pellagra,*" but at what time the term was introduced and by whom invented we are in complete ignorance. So far as the author has been able to determine, it first appeared in the literature in an article by Giovanni Strambio, in 1824, but it seems evident, from the way in which he alluded to it, that it must have been in more or less common use prior to this time.

The term is on the whole an unfortunate one, since it implies a relationship to typhoid fever that the facts fail to warrant. Whatever may have been the intention of its originator, its use would naturally carry the implication that this form of pellagra is etiologically associated with typhoid fever,—and we know that such was the opinion of certain pellagrologists of the past. As our knowledge, however, concerning both affections progressed, this view ceased to be tenable; while it must be confessed that there is no reason why typhoid fever should not develop in an individual suffering from pellagra, it is equally true that we may without difficulty conceive

of symptoms closely simulating the former occurring during the course of the latter disease, and in this category doubtless belong most if not all of our cases of "typhoid pellagra."

From a symptomatologic standpoint, however, there is no objection to the term, as it in a word carries to the medical mind the picture which it is intended to convey, and its use is convenient and unobjectionable if we remember that it is used only in a clinical sense.

As its name indicates, the typhoid type of this disease consists in a complication of symptoms that occur in the course of pellagra, characterized *by fever, diffuse diarrhoea, great loss of strength,* and *delirium,* with a tendency to *motor disturbances,* manifesting themselves in an *increase of reflexes, epileptiform attacks, convulsions, opisthotonus,* and almost always *terminating fatally.* The disease runs a shorter course than typhoid, and is not accompanied as a rule by enlargement of the spleen, or by a roseola.

The affection commonly comes on as a sequel of a chronic pellagrous cachexia, though in many instances it develops in the earlier stages. The writer has seen an instance where it occurred in a patient who had been previously in almost normal health, and who had never exhibited before any of the major symptoms of pellagra; in this case the first symptoms were psychic, there being delusions quickly followed by delirium, and subsequently the development of diarrhoea and the typical pellagraderms.

This peculiar form of pellagra was probably observed by all of the earlier writers on this subject, and was manifestly referred to by Strambio (4) in his description of the acute delirium to which reference has been already made.

However, the first observer who gave it special attention was Rizzi, whose well-known paper appeared in 1844. Following this the subject was discussed by Lussana in his classic works on pellagra,—he having attempted to prove that the disease is *simply a typhoid* occurring during the course of this malady.

This view was, however, combatted by Roussel (3), who quite correctly affirms that it was not considered a separate disease by Strambio, and it may be added that such was the view of Nardi (2), and at a later time of Verga (3), who called attention to the fact that this affection is not accompanied by enlargement of the spleen, nor by swelling and ulceration of Peyer's patches. Roussel (3) says, "There exists then during the course of pellagra a form, a phase, in a word a peculiar state which is not due to a complication by typhoid, nor is it an acute delirium the result of meningitis" (p. 76).

At a later time Lombroso (11) advanced the view that typhoid pellagra is in reality the result of *nephritic complication,* he having found quite commonly the evidence of this condition in the urine, and an increase of urea in the blood on chemical analysis.

Vassale and Bremer both have drawn attention to the frequency of kidney complications in insanity, a condition which the former writer has noted in six cases of typhoid pellagra.

Somewhat more recently Venturi has attempted to reconcile previous views on this subject by the assumption that some of the cases

of this kind are true typhoid, while others are due to other causes. This view he has attempted to substantiate by necropsies in cases of this kind, he having made post-mortems in seventeen instances. According to his findings he divides the cases into four groups:

(1) Those which he regards as *typical typhoid fever* occurring in pellagrous individuals.

(2) An acute febrile condition characterized by swelling of the mesenteric glands, which he calls *adeno-typhoid.*

(3) An acute febrile condition with no morbid alterations characteristic of typhoid, which he considers *true typhoid* pellagra.

(4) A variety of the affection which he regards as being *septicaemic.*

The most complete and thorough article which has heretofore appeared on this subject is that of Belmondo, who as the result of clinical and post-mortem studies in fourteen typical cases of typhoid pellagra comes to the conclusion that the disease is due to an increase in the pellagrous poison, and is to be regarded simply as a very acute and *severe type of pellagrous intoxication.*

As this author's description of the clinical phenomena of typhoid pellagra is perhaps the best which has as yet been written, it may be here quoted in its entirety.

"As a rule the morbid phenomena in these cases have previously existed for a number of years (2 to 5, and even 8); in some cases however it occurs much earlier; as in a girl of nineteen, who had been sick only a few days before her entrance into the hospital.

"In some cases the attack is sudden, but in the main the well-known symptoms of pellagra have regularly made their appearance in the spring for a number of years previously, but at this particular time come on with exceptional severity; the enteritis and nervous phenomena (weakness and pareses) take on an unaccustomed severity. There are likewise psychic manifestations consisting in a lowering of perceptive power and dulling of the conscience, usually depression of the spirits, accompanied by hallucinations, generally of sight, and a tendency to suicide. At this point there generally occurs motor agitation, with incoherence in acts and speech, and as a consequence the patient is brought to the infirmary.

"Here the patient exhibits usually a state of grave physical weakness and profound mental obfuscation, the legs do not support the body, and the patient is confined to the bed. As a rule the nutrition of the patients is bad, and they sometimes present marked emaciation; in others, however, the fatty tissues are still abundant and the muscular development nearly normal. Generally there is an almost absolute loss of consciousness, accompanied not uncommonly by verbigeration. The patient is evidently the prey of hallucinations, which are usually visual and of a terrible nature. His gaze is fixed in one direction, staring with terror; at times he attempts to leave his bed in order to escape the frightful visions, and, when capable of expression, he cries out at the sight of the terrifying illusions, particularly imagining that he is surrounded by flames that seek to consume him

(at times he has a true erytropsia). Nearly all of these patients sooner or later have the idea that they are soaring at an immense height, and desperately seize the edges of the bed and beg to be saved.

"All of the muscles are in a state of violent contraction, or at least there is a fixed state of the muscles of the belly and extremities which is perceptible on palpation. All passive movement is rendered impossible by the reflex rigidity which follows manipulation. On the other hand the patient from time to time executes incoordinate movements, particularly with the arms or hands. In the performance of these acts there is apparently an intention-tremor, with a certain degree of ataxia. The speech is drawling, the voice tremulous, and often nasal. The head is commonly drawn backward by strong contractions of the cervical muscles, and lies upon the pillow in a characteristic fashion, or at times is moved and convulsively agitated from left to right in a uniform and monotonous manner.

"Also the face has a rigid and fixed expression; at intervals however the muscles of expression, particularly those around the mouth, tremble and exhibit rapid fibrillary contraction, which extend from one group to the other or even to a distance.

"The legs are habitually in a state of forced extension, the feet in plantar flexion, the tendon reflexes are always augmented, even to the hour of death; the knee-jerk is particularly exaggerated. Not uncommonly there is also a peculiar phenomenon that occurs in the feet. In such cases a simple tap on the quadriceps provokes a diffuse clonus in the entire limb, accompanied by spasms in the whole body. Sometimes together with the foot clonus there are paradoxical contractions of the extensors of the feet.

"Together with this extraordinary neuromuscular hypersensibility there generally occurs a noteworthy hyperaesthesia, which becomes evident on stimulating the cutaneous nerves of touch, and even still more those of sensibility. Even a light breath, a noise, or a ray of light suffices to provoke disordered movement or automatic motions of defence or general spasms. Not always there likewise occurs hyperalgesia; also now and then the pupil no longer reacts to painful stimulus on the surface of the neighboring skin. On the other hand sometimes we find the cutaneous reflexes abolished. In one case there was a marked and prolonged vascular cutaneous reflex.

"Fever is rarely absent in typhoid pellagra. It is, however, irregular and atypical, there being no regular evening exacerbation. It does not reach usually a very high degree, varying between 101.3° F. (38.5° C.) and 104° F. (40° C.). In the last stages of the disease, after *decubitus* occurs, the patient may have high fever coming on very suddenly.

"There is sometimes insomnia, and on account of the unconscious condition of the patient, inability to take food, and the urine and faeces are passed involuntarily. In some cases, on the other hand, retention of the urine results from a paralytic condition of the bladder. The tongue is dry and cracked, and the teech covered with sordes. Commonly there is conjunctivitis (so-called neuroparalytic)."

All of the described phenomena aggravate rapidly, and in almost every instance the disease terminates fatally in the course of from one to two weeks, though occasionally the time is longer. During the course of typhoid pellagra there are now and then brief periods of improvement, in which the patient regains consciousness, is more calm, seems to improve, and a little food may be taken, but after a few hours he has a recurrence of the grave symptoms, and then sinks back into his former condition. Commonly toward the termination of the disease bed-sores occur, which every precaution does not prevent, and which extend rapidly. A short time before death foci of broncho-pneumonia develop, which are usually the immediate cause of the fatal termination.

HEREDITARY JUVENILE PELLAGROPATHIES.

As has been already pointed out, it was early recognized by students of this subject that pellagra is often hereditary, but it was only the cases that showed typical manifestations in early life that were so regarded by these writers. As the study of the subject progressed, it somewhat later became clear that this hereditary tendency is not alone manifested in the pellagra of childhood, but that it is clearly true that even in adult life the progeny of the unfortunate victims of this malady suffer much more commonly than those born of healthy parents.

No stronger proof of this tendency could be adduced than the statistics of Calderini; in 1,005 patients admitted to the city hospital of Milan from 1844-46 it was found that in 300 the disease developed before the end of the third year,—the proportion being one-fifth in the male and one-fourth in the female of the total number of patients examined.

The same investigator likewise determined that of the 1,005 cases referred to a history of heredity was obtained in 618 individuals, in 380 it was uncertain as to whether such influences played a part or not, and in only seven it appeared to be quite clear that the patients were born of healthy parents.

Of similar import are the statistics reported by Calderini from observations made by Ghiotti and Longhi. These investigators carefully examined 1,319 persons who were members of 184 pellagrous families, and found that 671 were healthy and 648 were victims of this disease.

It was likewise shown by this observer that there seemed a tendency for the affection to be more commonly transmitted by parents to children of their own sex, which would be quite in keeping with the observations of Ghiotti and Longhi, to the effect that the malady is more often transmitted from the mother than from the father. Calderini found that in 96 couples where father and mother both suffered from this disease there were one hundred and sixteen sons and one hundred and six daughters pellagrous; in 160 couples where the father was pellagrous and the mother healthy there were sixty-four sons and forty-nine daughters, but on the other hand in

175 couples where the mother was pellagrous and the father healthy there were born to them thirty sons and thirty-eight daughters who developed this disease. It is interesting to observe that these figures would seem to indicate that the disease is transmitted proportionately more often from the father than the mother.

The foregoing statistics by no means stand alone, since they have been abundantly confirmed by Agostini, Roncoroni, Marpurgo, Devoto, Antonini, Seppelli and Lui, Simonini, and others.

As evidence of the fact that pellagra shows a tendency to heredity in the new world, mention may be made of the fact that an interesting paper has been recently written in this country by Knight, who reported a father and mother and eight children all pellagrous.

As to whether the malady is transmitted directly from parent to offspring we are still not in a position to determine, though the author is strongly of the opinion that this is the case. That deleterious influences are directly inherited where the parents suffer from this disease is clearly indicated by the fact that the offspring frequently exhibits physical malformations, curious asymmetries in the nervous system, and in a great number of instances early shows constitutional deficiencies, all of which can be explained but in one way. Assuming the truth of the author's thesis, that practically all of the pronounced clinical manifestations of this disease are the result of organic change, there can be no reason, *a priori*, why such alterations may not occur during embryonic life, and why pronounced symptoms of pellagra should not develop in infancy,—particularly where the child has not been properly nourished or has suffered from acute infectious processes. While it is true that we have no direct observations bearing on this point, the author feels under the circumstances that the view just expressed may be tentatively advanced, not only as an explanation of the typical pellagrous attacks in children, but of the other symptoms of ill health that the offspring of pellagrins so often exhibit, and to which attention will be more particularly directed in the succeeding pages.

In order that this subject may be thoroughly investigated—and the possibilities appear enormous to the author—it is not only desirable that necropsies be made on the bodies of infants born of pellagrous patients who have shown unmistakable evidence of having this disease, but it is quite as important to examine carefully a series of cases, with a similar ancestry, where death is the consequence of the cachexias so common under such circumstances; it is highly probable that an inquiry of this kind carried out in a thorough manner would throw much light on our general knowledge of the pellagrous processes.

Whatever future investigation may show respecting the possibilities just enumerated, we have an enermous body of facts which now clearly indicate the tremendous rôle that heredity plays in this disease, and, as will be shown in the succeeding pages, it is perfectly clear that such tendencies are cumulative, and that the longer that pellagra exists in a community the earlier its victims are attacked and

the greater the proportion of cases where such influences cannot be doubted.

While the foregoing facts apply quite as much to pellagra in the adult as to the infantile forms of the malady, it is only with the latter that we are at present concerned, and our discussion will, therefore, be limited to the pellagrous manifestations in infancy and childhood.

Inasmuch as it has been shown beyond question that the physical anomalies, the constitutional weakness, and typical pellagra in the early years of life are but phases of one and the same fundamental condition, it is difficult and likewise illogical to attempt their separation. If, however, we will remember that they have a common etiologic basis, and that where one occurs a close examination will generally reveal the others to a greater or less extent, a consideration *seriatim* of the several phases of this early form of pellagra offers decided advantages from the standpoint of clearness of description, and will, therefore, be adopted in our treatment of this subject.

The division that seems natural and most helpful for the end in view is as follows:

DEGENERATION.—That the offspring of pellagrins not infrequently present stigmata of degeneration seems first to have been recognized by Sacchi. Later Lombroso (11) particularly called attention in such cases to *malformations* in the *development of the cranium*, there being either extraordinary *brachycephalism* or *dolichocephalism, recession of the forehead, abnormal position of the eyes, asymmetry of the cranial vault*, and *anomalies in the genital organs;* similar observations have been made by Gemma (2, 3), Roncoroni (1), Morpurgo, Devoto (2), Agostini (4, 5), Antonini (3), Dell' Isola and others.

Of much interest in connection with this subject are the observations of Antonini (4), who was able to determine that 59 of 157 cases in the pellagrous hospital at Bergamo were descendants of pellagrins; of this number 38, or 62%, showed degenerative characteristics, but in 98 patients, whose parents had never shown evidence of this disease, only 18, or 17.9%, exhibited such peculiarities. The degenerative changes cansist in the main of irregularities and asymmetries, such as abnormalities in the ears, of the skull, nose, teeth, etc. By a system of careful measurements he showed that the *capacity of the cranium was less* in hereditary pellagrins than in normal people.

Somewhat later similar observations were made by Seppilli and Lui, and Seppilli (3) alone. These writers found that in 173 insane persons 58% of them were the offspring of pellagrins, and that they not infrequently showed *malformations* of the *cranium and face*, and *pathological conditions* of the *throat*, and *rickets*.

Similar observations have been made by Bonservisi.

Lombroso (1)) has likewise written of what he regarded as atavistic manifestations in hereditary pellagrins.

HEREDITARY PELLAGROUS INANITION.—Of much greater interest and infinitely greater importance than the occurrence of physical anomalies is the fact that a large proportion of the offspring of pellagrins come into the world badly developed, and physically weak. Such children are but ill-equipped to withstand the lack of care, poor food, and unhygienic conditions to which they are for the most part subjected, and under such circumstances they fall victims in great numbers to the acute infections which are so common during the first years of life, or sicken, waste away, and finally die from digestive disturbances.

As has been already mentioned in the chapter on etiology, this condition appears to have been first referred to by Sacchi in the report of the Piedmont Pellagra Commission of 1847. This writer says that the children of pellagrins

do not *become* pellagrous, but that they are *born with the disease.* This condition is spoken of by him as a *habitus,* and antedates, he thinks, by a long time the development of the typical symptoms of the malady; it is indicated by the *vacillating* and *uncertain step,* the *yellow conjunctivae,* the *emotionless aspect,* the *pale and yellow color of the countenance,* the *redness under the eye brows,* the *chapped lips,* the *thin hair,* the *premature wrinkles,* the *undeveloped muscles,* and the *stupid* and *apathetic appearance of the victims.*

In the first edition of his book, published in 1869, Lombroso (2) likewise refers to the *imperfect development* and *constitutional weakness of the progeny of pellagrous ancestors.* He says that the condition is in some instances grave, while in others not so pronounced.

The former is manifested from the second year onward by the patient showing in some cases *desquamation,* and quite commonly *pains in the epigastrium, pyrosis, voracity, uncertain gait,* a *tendency to become frightened easily, diarrhoea,* a *yellow color of the skin,* and an *imperfect* and *tardy development;* at a later time the typical symptoms of pellagra may appear, and are always most tenacious and refractive to all methods of treatment.

He likewise calls attention to *malformations,* particularly of the head, *asymmetries* in the vault of the mouth and *anomalies* in the genital organs.

The patients often show atavistic symptoms, such as an *inability to fix the attention* and *bad memories.*

However, the first investigator who pointedly called attention to this condition of affairs and who recognized its occurrence in early infancy appears to have been the eminent pellagrologist Gemma (3), whose great powers as a clinical observer appear not to have been recognized by his contemporaries,—a fact doubtless in a measure the result of his sharp tongue and somewhat irascible temperament, which led him not infrequently into rather bitter controversies with his colleagues. This neglect in the present instance was doubtless also somewhat the result of Gemma's having broadly asserted that the 18 cases which he reported were instances of pellagra, when there was but little in the clinical histories to sustain the correctness of his diagnosis. Of the entire number recorded only 4 showed any skin changes; one exhibited epidermal scaling of the hands, and one of the forearm; the former was 7 months of age and had constantly eaten corn mush; in another instance the child had minute blisters on the side of his nose, and in the remaining case there was a slight erythema of the hands, which disappeared in 20 days. Practically in every case, with the exception of those mentioned, the diagnosis rested alone on the fact that the patients had digestive disturbances, but were the offspring of pellagrins. That all of these patients, save three, were in reality victims of the hereditary forms of the disease seems highly probable, since it is now well recognized that the symptoms from which they suffered are those most commonly observed in the children of pellagrins. The matter was not, however, in Gemma's day so well understood, and it must be recognized that he was indiscreet in asserting without qualification that these cases were pellagrous; under the circumstances one cannot but in a measure sympathize with the sharp criticism that Gemma was subsequently subjected to by Merk (1) for his attitude in this article, however undeserved it may have been on the whole. Let no one, however, for a moment suppose that this was in any way unexpected by Gemma, as he well understood that he was venturing into rather deep waters, and that he was certain to be taken to task for being somewhat in advance of his contemporaries.*

He was quite willing that the affections described by him be given some other name, as he observes that this would in no way change the facts. He even proposed that the condition be known as the *atrophy, anaemia, gastroenteric catarrh,* or *inanition in the descendants of pellagrins.* He says that he calls it pellagra for the reason that the disease is observed in the children of pellagrins,

*He says: "Perhaps no one will admit that the cases I have described are really pellagrous, since they exhibit so few of the symptoms ordinarily encountered in this malady." And then, with the air of a preux chevalier, he adds, "The scientists are quite commonly as difficult as the ladies. But both always find me most complaisant."

because there occur intestinal, dermal, muscular and nervous phenomena, and because the malady is amenable to the treatment ordinarily employed in combatting this disease; he states that in the only three instances observed by him where the affection did not appear to be hereditary, two of the children had been nursed by a pellagrous woman, and the other had been always fed on maize meal mush.

This acute observer noted that the *cranium* in hereditary pellagrins is usually *larger than normal,* but says he has never seen retardation in the development of the teeth. In some cases the patients are fairly well nourished, but very often are emaciated and *present enlarged lymphnodes.*

One of the common symptoms, according to Gemma, is a *roughness of the skin of the forearm and of the cheeks,* which is best felt by the little or ring finger, as he thinks that the sensation is here more acute than in the other fingers, or even in the lips; in the same situation minute fissures in the epidern may be observed with a hand lens. The skin is usually *pallid,* but occasionally a *redness* of the cheeks and nose may be observed, which will be found on close examination to be the result of dilitation of the superficial capillaries; in the same situations, as the child grows older, the skin has a smoky appearance, becoming more marked with age.

The lips, if not presenting a livid appearance, are usually of a *vinous red color,* the eyes *lachrymose,* the *conjunctiva pale* or *red,* and the *papillae strongly developed.* Toward the end of the *tongue minute red spots* representing the apices of the papillae are likewise observed.

The *muscles are weak,* the *limbs support the body badly,* and in young children the *head hangs to one side.*

The children often show *bulemia,* but quite as frequently have a *distaste for food.* The *appetite* is *capricious* and *vomiting* is not uncommon.

Diarrhoea is very frequent, the stools being *liquid,* generally *green,* and of *acid reaction;* sometimes there is *mucus* and even *blood* mixed with the fecal matter.

Ordinarily the *belly* is soft, but frequently more or less swollen with gas; sometimes the *liver* is slightly enlarged.

Gemma (3) particularly calls attention to a peculiar "blowing or bellows" respiration, which he says is exceedingly common in this condition. The respiratory act is *rapid* and *difficult,* accompanied by *dyspnoea* and *true pellagrous asthma.*

The *mental faculties* of such children are clèarly below the normal, and they become indifferent, and cry without cause. In some instances it seems that they develop a real *psychosis,* if we may judge from their actions. Frequently they suffer from *insomnia.*

The *pulse* is *normal,* and the *temperature* often *below normal,* though it is occasionally *elevated.*

The foregoing symptoms are particularly common in the *spring,* though they may also develop in the *autumn.*

Under proper treatment the patients usually recover.

Following the paper of Gemma nothing more seems to have been done on this subject for a number of years, when the subject of hereditary pellagra was taken up by Seppilli and Lui, who appear to have been the first to formulate the modern view of this subject. By *hereditary pellagra* these authors understand a *transmitted degenerative condition in which, as may be the case with alcoholism and certain chronic intoxications, there occurs essential modifications in metabolism and in the functionating power of the nervous system, determining in the descendants of pellagrins a weak constitution, and producing a state of lowered resistance, which leaves the individual especially susceptible to the maize toxines.*

However valuable the contributions of the preceding writers may have been, it was really Agostini (14, 5) who first gave this subject prominence in the literature, and who brought forward irrefutable proof of the terrible nature of the heritage bequeathed to their offspring by pellagrous ancestors.

In his well-known first paper on this subject, which appeared in 1902, Agostini says:

"The children of pellagrins have a *mortality of* 45%, and they exhibit an *abnormal conformation of the head, asymmetry of the face,* an *old appearance*

and *marked retardation in growth, bad development of the tissues* and *chronic gastroenteric catarrh.* When they survive the first infancy they retain the pellagrous cachexia and have *retardation of the development of puberty,* and *anomalies of the genital organs. Congenital hernia* is common. Two cases of *pseudo-myxedematous infantism* were encountered, as were also two instances of *dystrophic infantism,* for which the name of *heredito-pellagrous infantism* is suggested, the condition being characterized by *retardation of mental and physical development,* a *low statue, scanty growth of hair, delicate limbs, prominent bellies, rudimentary testicles, yellowish skin,* and a *violaceous color of the mucous membranes;* in those cases where the thyroid gland is altered in volume there follows *cachexia* and *atrepsia,* and a *physiologic misery,* which leads to arrest of development, as a consequence of which the fundamental characteristics of infancy are prolonged."

Agostini further speaks of a child three years of age—whose mother was healthy, but whose father was pellagrous—which presented the appearance of premature age, and whose head was hydrocephalic; there were also swollen tissues, lack of teeth, violaceous mucous membranes, and a chronic gastroenteric catarrh.

In a later paper this author (5) comes to the following conclusions respecting this very important subject:

"Maize intoxication of the ancestors—particularly of the mother during the period of gestation and nursing—induces in the offspring an *early weakness* and *frailty,* a *tendency to disease, retardation, deviation,* and sometimes *arrest of development* of the body, even to the *last degree of somatopsychic degeneration,* to *idiocy, dwarfism,* and *sterility.*"

"These unfortunates present an *especial predisposition to ordinary pellagra,* and are particularly prone to become *insane;* the condition is also one of the most common factors as a predisposing element in causing constitutional neuropathies and psychopathies."

"This slow and progressive hereditary degeneration *has already induced an evident and noteworthy imperfection in the bodies of the people inhabiting the zones where pellagra is most diffused and common, and has resulted in a great augmentation of mortality in these subjects;* there is an ever increasing population of the physically weak who have an increased tendency to disease, and who suffer from dystrophies and bodily infirmities which make them unfit for military duty, and a large percentage of which are fatally destined to populate the homes for the poor, the hospitals and the asylums,—the subjects of an economic and social canker which is progressive and without bounds. Most of the *young women do not menstruate before the eighteenth year,* and this is accompanied by *vertigo, headache, irregular pains,* and *frequently leucorrhoea;* the *limbs are lean,* fat being almost entirely wanting, lack of harmony in the lines of the body, and a *profound anaemia,* all combining to produce a state of misery that robs its victim of the physical beauty which is the only attraction of the daughters of poverty. The *male hereditary pellagrins* are usually of *low statute,* and with *disproportionate limbs;* there is *asymmetry of the countenance* and in the *formation of the cranium,* along with *bad development of the muscles of the extremities, thinness of the trunk, malformation of the thorax, distended abdomen,* and frequently *congenital hernias;* there is commonly a *scarcity in the development of hair.* Up to nineteen years of age *one-fourth of these unfortunates show rickets.*"

During the first three years of life the pellagrous child not uncommonly dies of *marasmus,* or as a consequence of *spasms,* both of which are probably the result of the gastro-intestinal catarrh. The pellagrous child has the appearance of *ill-health,* an *old look,* along with *thinness of the body;* they are *born small,* with the weight and length of body below the normal, they have an *incomplete* and *slow growth,* so that even at the third or fourth year they are often still unable to support themselves on their feet, and are just beginning to lisp a few syllables; at this period dentition is just beginning, the *head* is *large* and *pseudo-hydrocephalic, badly formed,* with the fontanelles open to the sixth or seventh year; the face is *rachitic,* and there often protrudes from the small neck an enlarged thyroid, or, not infrequently, this gland is smaller than normal. The *thorax* is *rounded,* with the *sternum prominent,* and the bulging costal arch extends below to the swollen and frog-like stomach; the *umbilicus protrudes.* The small muscles show prominently over the large joints, and the *skin of the face is*

yellowish, wrinkled, dry, and *oftentimes edematous.* The *lips* are *bluish* and frequently present *ulcerations;* the *tongue* is *large* and *catarrhal;* the child suffers usually from *diarrhoea,* accompanied by dilitation of the stomach and intestines. He is *sad, querulous,* and *scarcely sleeps* during the night. The *milk* of the mother is *unsufficient* in *quantity* and *deficient* in *quality,* though analyses do not show that it differs materially from the normal,—with the exception that there is usually an *increase in salts,* and a *diminution in casein;* whether the result of chemical deficiencies, or the consequence of the presence of poisons in the aliment there unquestionably results a *catarrh of the intestinal tract* of the child, frequently accompanied by *convulsive phenomena.*

In a subsequent paper the same author (7) continues his studies of this subject, and notes that pellagrous insanity is on the increase in patients admitted to the sanitarium for the insane at Brugia.

In Umbria he found evidence of *degeneration in 67%* of all hereditary pellagrins. In addition to the very common *hydrocephalus* this investigator also noticed in these unfortunates a *fronto-parietal plagiocephalia, undue prominence* of the *frontal eminences, protruding zygomata,* and *anomalies* of the *teeth;* there were also frequently present *deformities* of the *vertebral column,* of the *thorax,* and of the *limbs.* In this article the writer lays still greater stress on the frequency of *disease of the thyroid* in these cases, and the common occurrence of *muxedema* and *cretinism.* He speaks of a case with *absence* of the *mammary glands* and *dwarfism;* the height of one patient at 34 years of age was only 1.17 metres (46.06 inches), and there was *complete dystrophy* of the *sexual organs,* and *absence* of *menstruation* and a *general deformity of the entire body.*

This author insists that the frequency of thyroid disease among the Italian peasantry is a logical consequence of maize intoxication.

He likewise calls attention to the fact that *hereditary pellagrins are peculiarly susceptible to the maize poison,* that is, they are unusually prone to become typical and frank pellagrins.

The mortality in these unfortunates up to three years of age exceeds 50%. The writer notes that with the advance of time the *age at which patients become pellagrous gradually becomes* less, and that while insane pellagrins under twenty years of age were rare in the asylum at Perugia thirty or forty years before, the number is now quite considerable, many of them being under ten years of age.

In this connection Antonini (4) has given some interesting figures, he having shown that in 100 non-pellagrous families there were born 616 children, of whom 200 died, and 416 were still living at the time the inquiry was made; the mortality was 32.47%. In 100 pellagrous families on the other hand there were born only 523 children, of whom 225 died, leaving 298 living at the time the figures were obtained, the proportion of deaths being practically 43%. It was likewise true that in the healthy families there had occurred 19 abortions and 7 still-births, while in those that were pellagrous there were 32 abortions and 15 still-births.

Camurri (6) has likewise discussed the question of hereditary pellagra. This writer believes with De Giovanni that there exists an *organic predisposition to pellagra,* but he was unable to convince himself that the disease itself may be directly inherited. Children showing this unhappy tendency are characterized by the *largeness* of their *heads,* which frequently *wag from side to side, prominent veins, imperfect deevlopment of the body,* a *small but long thorax,* and *short lower extremities;* they are *stupid* and *anaemic,* frequently suffering from *vomiting* and *diarrhoea,* and not uncommonly *die before the seventh year.*

As mentioned in the chapter on the pellagrous psychoses, Agostini (7) and Valtorta (3) have studied the mental changes characteristic of hereditary pellagrins. The former observer distinguished two classes of cases, the one being a *congenital mental deficiency,* varying from slight intellectual weakness to complete imbecility, and the other characterized by simple *melancholy* and *mental confusion,* and not uncommonly associated with *hypochondria, nervous disturbances, hallucinations, anxious melancholy, delusions of persecution,* terminating in a *stuporous* or *tranquil dementia.*

The latter writer observed in a few instances *dementia* preceded by *confusion* and *hallucinations,* and in others by symptoms of *manic-depressive insanity.*

The most complete and thorough work on the subject of hereditary pellagra is the very extensive monograph by Simonini, published in 1905.

After quoting the results of the work of previous writers this observer takes up the subject of the effect of pellagrous parentage on children at birth. He has calculated that the normal child on an average at full-term weighs 3,000 grams (96.46 oz.=8 lbs.-|-), but he has found that of 152 pellagrous infants at birth only 37 reached this figure, 9 weighed somewhat more than 3,250 grams (104.5 oz.), while the larger proportion did not exceed 2,800 grams (90.03 oz.); 14 cases reached 2,500 grams (80.4 oz.), 4 1,900 grams (61.09 oz.), 11 1,780 grams (57.2 oz.), 3 1,490 grams (48 oz.), and 7 1,270 grams (40.83 oz.). Of the 152 children 112 were nursed by their mothers, 5 were placed in the hands of healthy wet nurses, and the others were fed on milk more or less diluted with water; of the first series 48 reached the fifteenth month, while in the others the children began to fail immediately after birth, and for the most part were carried off by various diseases, among which were *dyspepsia, acute* and *chronic gastroenteritis, bronchial pneumonia,* and *spasms;* of the last series only 1 lived to the twelfth month; of the 5 put out to nurse only 1 died, this result being the consequence of a *broncho-pneumonia* following influenza. In general these children *showed little resistance to disease,* and almost all exhibited *rickets* very early.

The blood of a number of these infants examined from 2 to 7 hours after birth showed little of importance, though occasionally there was a silght elevation of mononuclear leucocytes (21% to 28%).

In 16% of the cases the *rectal temperature* was found *below normal,* and the subjects generally showed evidence of *poor development.* They *never exhibit* the gradual and normal *increase in weight,* even if they are nursed at their own mother's breast; not uncommonly *acetone* is present in the *urine,* as is also *butyric* acid, which is derived from disintegration of the fats and proteids of their bodies.

This writer presents a table showing the increase in weight in 5 pellagrous children during the first week,—one of which died on the sixth day and another at the end of the thirty-fourth day. The *increase in weight is much below the average,* being during the first three days about half the normal. Simonini thinks that this is the consequence of imperfect digestion on the part of the infant, and also, perhaps, likewise of certain abnormalities in the mother's milk.

He has made a number of analyses of the *milk of pellagrins,* and finds that in addition to the *increase in salts* and *diminution in casein,* first noted by Agostini, there is also a *defect in its iron content.* He thinks it extremely probable also that there are *toxic principles* in the milk which defy chemical analysis. This writer is therefore strongly of the opinion that the *pellagrous mother should not nurse her child.* This he thinks is better than making special provision in the matter of good food for the mother during the period of lactation, as urged by Tambroni, as these unfortunates generally suffer from gastrointestinal disturbances, and are really not in a position to assimilate properly.

In addition to the disturbances to which reference has already been made the writer notes that *perversion of taste* seems very frequent in pellagrous children, and that earth eating has been found to exist in about 27% of the cases.

The coëxistence of *intestinal parasites* is also extremely common, the hookworm occurring in 80% of all cases.

Also quite irrespective of the extraneous causes the hereditary pellagrin presents *oligaemia, anaemia,* and *chloro-anaemia* in the great majority of cases.

This author has particularly found chloro-anaemia common in hereditary pellagra, even in early infancy and at a period when this condition could not be the result of earth eating, or the consequence of hookworm infection.

Physical examinations of these patients show that the skin is *yellow* and *very pale,* the *tissues soft* and *flaccid,* and *haemic murmurs* are common in the third intercostal space on the left side and in the veins of the neck.

On examining the blood it is found that there is a *slight diminution in red cells* and an *enormous decrease in the haemoglobin,*—this substance going down as low as 20% in some instances. It is noteworthy that this anaemia does not develop quickly after birth, but occurs generally after the twelfth month when the reserve of iron and other proximate principles of the body present at birth have gradually diminished as a consequence of imperfect food and bad digestion.

Where hereditary pellagra is repeated and exaggerated by its occurrence in generation following generation the somatic alterations become more and more pronounced, and the psychic degeneration is accentuated to such a degree that the unfortunate victim frequently presents divers grades of mental atrophy not uncommonly accompanied by *nanism.* This author observes that the most frequent mental change appears to be a *psycho-asthenia,* with simple *mental deficiency* or *idiotism,* with complete imbecility of a melancholy type, and not infrequently *epilepsy,* with *hysteria* and *neurasthenia.* In a few instances *dementia* with *stupor* and *hallucinations* and *melancholia* occur.

It is likewise observed that paraesthesias of various kinds are not uncommon, being usually referred to the viscera, particularly the stomach and intestines, and while changeable are frequently persistent and so disturb the patient that he becomes *hypochondriacal.*

This author, following Agostini, DeGiovanni, Devoto, Lucatello, and others, stresses the view that *hereditary pellagrins are more susceptible than others to the ill affect of maize toxines. As would naturally be supposed, infantile pellagra is most common in those districts where pellagra has existed for a long time.*

Reference is made to the fact that the clinical forms displayed by hereditary pellagra depend in a great measure on the age of the patient, on the climate, and the general surroundings.

Thus it is true that in nurselings, and during the first years of infancy, the malady manifests itself preëminently in *gastrointestinal disturbances,* there occurring *diarrhoea* or *obstinate constipation,* or, in some instances, the two alternating with each other.

As the child approaches puberty *disturbances* of the *nervous system* are more common, resulting oftentimes in a clinical picture which is quite peculiar and characteristic.

The frequency of cutaneous manifestations is influenced by the character of the country, such *changes being more common on the plains, where it is warmer, than in the hills and mountains.*

The development of severe symptoms in these cases is frequently preceded by attacks of influenza or malaria.

The author very properly takes the position that skin symptoms are by no means a *sine qua non* in the diagnosis of infantile pellagra. In a study of 214 cases this symptom was only noted in 63 instances, while all exhibited *changes* in the *blood, disorders of the digestion,* not much less frequently *atrophy* and *marked malnutrition,* and *nervous disturbances* of varying form and intensity.

Testi has reported two cases of typical lateral salerosis in children of pellagrous ancestry.

From the foregoing it seems certain that there exists a condition in the offspring of pellagrins, which, whether called pellagra or not, is one that is *accompanied by profound abnormalities in development, beginning during embryonic life, and continuing throughout the period of growth;* in such patients there likewise often develops certain symptoms which strongly suggest pellagra, there being particularly *gastrointestinal disturbances, followed by general inanition, alterations in the skin,* and the *development of a variety of nervous symptoms.* It seems quite certain that such manifestations are becoming more and more common in those countries where pellagra is general, as is evidenced by the fact that that very acute observer, Gemma, who first described this condition, made mention of no abnormality in development except enlargement of the head, and that the clinical manifestations described by him were of a much milder character than are observed in Italy at the present day.

From the standpoint of symptomatology, and morbid anatomy and histology, these cases deserve the most careful consideration of every medical man, and since they are more likely to be uncomplicated by extraneous morbific agencies, *it seems not improbable that we may hope here to observe the really characteristic symptoms and pathologic changes which are wholly due to the pellagrous poison.*

As already indicated, we have in a certain proportion of cases development of what may be *regarded as typical pellagra in children,* though this is by no means so common as the somewhat anomalous forms which have been described in the preceding pages. The subject is one however that merits our attention, and will now be briefly considered.

TYPICAL PELLAGRA IN CHILDHOOD.—Pellagra in children is probably always hereditary, or at least the conditions that conduce to its development are unquestionably derived from pellagrous ancestors. In a small proportion of cases no such influences can be definitely determined, but it seems under such circumstances not at all improbable that a thorough investigation would reveal at least a latent condition of this kind either in the parents or grand parents. The age at which the disease may develop is still a matter of discussion. Strambio (4) says, "Not all but the greater part of the children of pellagrins show signs of this disease at a tender age, at a time when the causes could not operate that produce the disease in the adult" (p. 38). On the following page he says, "I have likewise seen it in children, nay even in nursing infants." Zecchinelli says that at first the disease did not occur in children, but in the course of time the affection became more and more frequent in youth,—it being finally common in infants of 2 or 3 years, and then even some were born with it. Other writers of this period likewise advert to the occurrence of pellagra in children, but there is much uncertainty as to the true character of the morbid states to which they referred. Almost a hundred years was yet to pass before the atypical hereditary forms were to be described by Gemma, and a still greater period was to elapse before there was anything like general recognition of this form of the disease. Whether the old pellagrologists accepted a general ill state of health with intestinal disturbances in children as being evidence of this disease, or whether they actually saw typical forms of the malady must forever remain a matter of uncertainty. That the former supposition is more likely correct is, however, strongly borne out by the facts which are a matter of common knowledge at the present day.

Some years ago a case was reported by Cristoforetti, which was also seen by Merk (1) and other competent pellagrologists, in which all of the typical symptoms of pellagra were found, and in which it seemed quite clear that the first symptoms appeared about the ninth month, though the baby was not examined until some five months later; this case is recorded by Merk as being undoubtedly the earliest well-authenticated instance of this kind on record. It is noteworthy that both father and mother were pellagrous, and that the patient was weaned at three months, after which it was thereafter fed on a mixture of maize mush prepared with milk and water. As we have in this case both the pellagrous ancestry and the history of maize eating at a tender age, it becomes a matter of impossibility to determine as to which of these two factors predominated in the production of the disease; Merk thinks that it is unquestionably due to the diet, but it is by no means certain that his *dictum* in this matter should be accepted. On the whole it appears not unlikely that the pronounced pellagrous ancestry probably had far more to do with the production of the disease than the short period during which the baby had eaten Indian corn, though it is not impossible that the manifestations of the malady were hastened and accentuated by a dietary almost wholly composed of this cereal. It is noteworthy that of the four children born to the parents two were clearly pellagrous, one being the case under consideration and the other, a sister, who had a marked hydrocephalus and had exhibited an erythema on the back of the hands in the spring for three years.

Some years ago Sambon, after several days of very careful investigation of the subject in Italy, announced that pellagra is an exceedingly common disease in children, and that the supposititious parasite is conveyed from the little ones to adults by an intermediate host—imagining it to be the common gnat—just as it has been shown that malaria is frequent in the young without occasioning marked symptoms, and that these early cases often become foci of infection.

Incited by the awakened interest in pellagra which followed the discovery of this disease in America, a commission was some years ago appointed by the Italian minister of the interior for the study of this affection; the commission was composed of Lustig, Alessandrini, Antonini, Bertarelli, Gianelli, Gosio, Sclavo, Tizzoni and Caetani, all being medical men with the exception of the last named.

Among the first subjects studied was the frequency of pellagra in children, upon which two reports have been made.

Preliminary to this investigation it was ascertained that pellagra was common in 34 of the 69 provinces in the Italian kingdom, and careful observations were

made in 22 provinces where the disease was reported as being most common. The total number of children examined does not appear in the records, the figures having been given only in five instances, where 17,019 observations were made. As the result of this most extensive investigation *not a single case of undoubted pellagra was found in a nursing child;* the disease was suspected in 4 cases, but the diagnosis was by no means certain; one of the cases was called by the commission doubtful, another very doubtful, and the remaining two simply suspects. It would thus appear that the occurrence of typical pellagra in infants is quite as imaginary as the supposed parasite, however clear it may be that the offspring of pellagrins frequently suffer from gastrointestinal disturbances and inanition, which we may regard as instances of this disease, or not, depending upon our view-point.

Simonini divides the pellagra of childhood, accompanied by the classical manifestations of the disease, as follows:

(1) Cutaneous form.
  (a) Pure.
  (b) Mixed.
(2) Pellagra without skin manifestations.
  (a) Gastrointestinal form.
  (b) A form characterized by cachexia, atrophy, and anaemia, with or without lesions of divers organs.
  (c) Nervous form.

Depending upon their course any of these various varieties of pellagra may be *acute* or *chronic.*

Especial attention may be directed to the fact that the class of cases now to be considered are not alone characterized by their nearer resemblance to the classical pellagra of adults than is the case with the so-called hereditary pellagrous inanition already considered, but that, in addition, the disease as a rule occurs in *much older subjects,* is more apt to *manifest itself in the spring,* is *preceded by some weeks of depression,* during which the victim suffers from the class of disturbances characteristic of the first stage of the disease in adults, and the *attacks are more prolonged.*

Prodromal symptoms.—Fortunately the clinical manifestations exhibited by the more typical types of the pellagra of childhood show such close resemblance to the malady as it occurs in the adult that a very brief description only is necessary.

As in the pellagra of adults, we have here also prodromal symptoms which begin some weeks before the disease frankly manifests itself. There is a *loss of vivacity, lack of interest,* and a *tendency to fatigue,* which is entirely foreign to the growing child; he becomes *gloomy, taciturn,* and *melancholy,* and *ideation, initiative* and *memory* are *less active;* there develops a sense of *weariness* and *weight* in the legs; sometimes there is *formication, burning,* and *other unusual skin sensations.* A *strong and progressive diminution in affection* is thought by Simonini to be very characteristic. *Choreiform movements* are not uncommon, and along with these a *feeling of weight in the head* and *vertiginous sensations,* which is not quite the true vertigo of the later stages, and which was well described by Fanzago as "balordone"; there is often a sense of *rotary movement,* the patient feeling not alone that *he* is turning around, but that *surrounding objects* do so as well,—this being quite marked when the patient suddenly rises from a kneeling or sitting posture; this sensation may be produced by causing the patient to make rapid backward and forward movements. This phenomenon appears to be nearly related to that noted by Leube in people with stomach and intestinal troubles, which is produced by making pressure upon these organs while the patient is lying on his back, and then rapidly raising him to an erect posture.

The cutaneous form.—The cutaneous form of the pellagra of childhood is divided by Simonini into two forms, the *pure* and *mixed;* within the former is included those cases where the skin lesions alone appear, or in which they completely dominate the clinical picture: the second form is that in which, while skin lesions exist, there likewise occur marked disturbances of the intestinal tract and of the nervous system.

Inasmuch as skin lesions occur in both of these forms, and since they only differ in that the other typical pellagrous phenomena are added in the cases belonging to the second group, there seems no good reason why they should not be described together.

The *skin manifestations* differ in no way from those observed in the ordinary pellagra, generally making their appearance symmetrically on those parts of the body that are ordinarily attacked, and lasting from 12 to 35 days, with an average from 16 to 20 days. *Diarrhoea* is usual, but *constipation* may occur. *Anaemia* and *chloro-anaemia* are common; in 58 cases examined by Simonini these conditions were found in 53, accompanied by *general debility, bad nutrition, continuous headache* in 2, and *periodical headache* in 7, *formications, cramps, paraesthesias* of various kinds in 39, *vertigo* in 2, *spastic difficulty in walking* in 4, *marked exaggeration of the reflexes* in 34, *mild diarrhoea* in 44, *constipation* in 12, *diarrhoea* and *constipation alternating* in 10; *paralyses* or *palsies* did not occur.

The second stage comes on in from *10 to 18 days*, which is earlier than in adults.

It is rarely the case that *pronounced inflammation* occurs in the skin, or that *deep fissures* form, but when this occurs it is invariably in severe forms of the disease. The skin lesions may terminate in *simple eczema*, or there may be *local* or *general suppuration*. In the severer forms of the malady there may be *profound alterations in the gastrointestinal tract*, with *profuse diarrhoea* and *nervous symptoms*, accompanied by *great debility, profuse sweating, somnolence, melancholy, hypochondriasis*, and *stupor;* there may be in addition *great excitability, impressionableness, logorrhoea*, and *mutism*, associated with a *decrease in tactile* and *thermal sensibility, paraesthesia, vasomotor disturbances, neuralgias, profound exaggeration of the reflexes*, and *spastico-paretic walk, increased muscular tension, disturbances of urination, general muscular atrophy*, and *edema of the face* and *lower extremities*. Occasionally spinal troubles are simulated, the patient appearing to be the victim of a *spastic paraplegia*, or in other cases of an *anterior poliomyelitis*, with *spastic phenomena* predominating.

The condition lasts for a variable period of time, depending entirely on its severity.

Where only a mild hyperaemia occurs on the backs of the hands there is only a *slight desquamation*, with rapid recovery. The exudate which occurs in more severe cases may be *serous, hemorrhagic*, or *sero-purulent*, and is contained in blisters formed by fluid raising the epiderm; this liquid may be absorbed, or the blebs may break, leaving ulcers. Where the process is severe it is followed by more or less *pigmentation*.

Simonini thinks the skin changes more or less correspond with the severity of the disease, though this is not true of adults.

There are rarely observed in childhood skin alterations which may be characterized as *erysipelatous, pimphigoid, seborrhoeic*, and *hemorrhagic*.

Clinical examination gives much the same results as in adults. There is usually *anaemia*, with some *increase* in the *white cells*.

Albuminuria sometimes occurs.

Hydrochloric acid and the *gastric ferments* are usually diminished or absent.

Simonini found *ammonuria* in 6 cases out of 9. There is no great increase in the *sulphur compounds* in the urine; occasionally *acetone* is found.

The *patellar tendor reflex is always accentuated*, which remains even after the plantar reflexes diminish and disappear; the pharyngeal and abdominal reflexes remain normal. The pupillary reflexes were found tardy alone in 2 cases.

The *faeces* are somewhat *liquid*, and of a *yellowish* or *yellowish-green color*, always *copious*, and frequently *fetid*. The bacterial flora in severe cases seem to be increased in virulence, as shown by injections made in animals.

The *heart* is weak.

The *temperature* may be normal or slightly increased. This does not occur with regularity.

Sometimes these *symptoms become chronic,* particularly the digestive disturbances, and as a consequence the patient becomes lean, cachectic, and may ultimately die.

Pellagra of childhood without skin manifestations.—Simoni is a confirmed believer in *pellagra sine pellagra in children.*

After the usual period during which *prodromal symptoms* occur, the patient may develop *pronounced intestinal disturbances,* accompanied by the diarrhoea usual in such conditions, and at the same time he presents the milder *nervous phenomena* which are inseparable from this affection.

In some instances the patient becomes *anaemic,* just as he may in the adult forms of the disease, and develops a *cachectic state,* which may terminate fatally; it is likely true that this condition is largely determined by disease of the *bone marrow.*

There also occurs a type in which *nervous manifestations* play the predominant rôle, these occurring in frequency in the following order: *hypochondria, formication* and *tremor, deficient mentality, headaches, neuralgias, stupor* and *moral depression, various paraesthesias, mental confusion, tetany, hysteria, arrest of mental development, epilepsy, cramps, cardiac palpitation,* and *hydrocephalus.*

Prognosis.—Prognosis in these cases is far more favorable than in adults, there being comparatively only a small percentage that die. This is well shown in the statistics of Trimble.

Treatment.—The therapy of the pellagras of childhood is in the main dietetic, and will be considered in the chapter devoted to the treatment of the ordinary forms of this malady.

METABOLISM.

As might well be assumed, *a priori,* from our knowledge of the disturbed digestion and greatly altered organs and tissues of the body, there is a profound disturbance of metabolism in pellagra. Just how great the variation from the normal may be we are unfortunately not in a position to judge with certainty, since at best our methods of determining conditions of this sort are crude, primitive, and even in some directions are non-existant. Our knowledge then of the chemical changes going on in the body is of necessity limited to the results observed from some few experiments bearing on the gaseous metabolism of the lungs during respiration, a moderate number of fairly exact examinations of the faeces, and quite a number of careful analyses of the urine, which, at least, inform us as to the alterations that occur in its principal constituents.

As practically all European pellagrologists are in accord as to the close relationship that the consumption of maize bears to pellagra, no apology is necessary for first calling attention to certain disturbances that occur in animals when this cereal is eaten.

As long ago pointed out by Balardini, and later by Lombroso, Antonini, Bezzola, Brugnola and others, the continuous consumption of this cereal for any considerable length of time produces in the *bodies of animals a profound cachectic condition,* accompanied by paresis, loss of hair, intestinal troubles, ataxia, and in some cases death,—this result occurring in the experience of the author in every case if the feeding with maize products be strictly adhered to and continued sufficiently long; just what takes place under these circumstances has, however, never been determined, but that the grain produces a chronic intoxication would be indicated by the symptoms, as well as by the pathological alterations described by Sereni, which occur under these circumstances. The fact that Antonini (8) produced more or less similar changes in animals by means of a mixed vegetable regimen, and by Blosser with an exclusive diet of sweets, in no way detracts from the importance or significance of the facts just recited.

We have likewise evidence that digestion and assimilation are frequently profoundly affected by a maize diet, though such results do not appear to be uniform. Thus it was found by Rubner that 19.2% of the nitrogenous food

passes through the intestines undigested where the diet consists of maize products exclusively,—the figures agreeing closely with those of Malfatti, who under similar circumstances determined that 18.3% are lost. It should not be forgotten also that Szumowski and Kossel and Kutscher have shown that zein is mildly poisonous to animals. It is interesting to observe that Nitzescu has recently stated that maize two or three years old is much more digestible and assimilable than the fresh grain. Baglioni and Audenino have determined that guinea pigs die in from two to three weeks when fed exclusively on maize, but such results have no particular importance in this connection, since it had been long before shown by Magendie, and still later by Dönhoff that all foods seem to produce rapidly poisonous effects, followed by death, when fed alone to any animal. Thus it is true that DeGiaxa observed that where normal persons were given 108 grams of albumin a day, entirely supplied by a diet consisting of maize and beans, 27.4% of the proteid was eliminated with the faeces. In criticism of these results it may however be remarked that only three persons were employed in these experiments, and that in all likelihood a considerable part of the undigested nitrogenous food was derived from the beans, as it is notoriously true that the proteids of this group of vegetables are difficult of digestion; on the other hand a diet of this sort is not at all unusual in the peasant classes in southern Europe, and after all may be fairly representative of the food upon which many pellagrins subsist. This writer as a result of many experiments comes to the conclusion that the peasantry generally receive *far too little albumin;* it must however be remembered that DeGiaxa's paper appeared during the period when the amount of nitrogenous food thought necessary was very high, and before the erroneous ideas of the past respecting this matter were corrected by the brilliant researches of Chittenden.

It was also noted by Camurri (3) that the presence of maize in a dietary more or less influences the metabolism.

On the other hand Devoto (2), with the assistance of Moreschi, likewise gave this matter careful consideration. He selected 3 pellagrins to whom he administered daily 250 grams of mush, gradually increasing the amount to 1,000 grams, and on making careful chemical analyses found that *there was no sensible modification in the amount of nitrogen absorbed* in two cases, while in a third there was *actually an increase* in the assimilation of this substance. It is therefore concluded by this able investigator that the use of *good polenta as a food by pellagrins without intestinal complications does not result in a disturbance of the digestive functions, provided the amount remains within reasonable limits.* The foregoing is in entire keeping with the statement made by Teboldi and Alpago-Novello to the effect that they cured 40% of their pellagrins with a generous diet of good maize.

It should not be forgotten also in connection with the alterations of metabolism produced by maize that Zuntz has shown that a diet of this kind results in a *25% increase of the output of carbon dioxide with the expired air,* and naturally in a corresponding increase in the absorption of oxygen.

We will now take up the consideration of the general metabolism of pellagrins, studying simultaneously the urine and faeces, a method of examination from which we at present obtain practically our entire knowledge of the nature of the chemical changes that go on in the body.

It was long ago observed by Calderini (2) and Verga (2) that the *quantity of urine passed by pellagrins* is in *general decreased,* and that the *reaction* is *usually weakly acid* and *sometimes alkaline,*—facts which subsequent investigation has abundantly confirmed.

The first attempt to investigate the urine chemically appears to have been made by Morelli, who found that the *urea* is *diminished* in this disease.

The first investigator however who made anything like an extensive examination of the urine by modern methods was Roncoroni (3) in 1890, who showed that the quantity of *urea eliminated is considerably less than normal in pellagrins,* and also that the percentage as compared with the body weight is below the average.

This matter has been further given particular attention by Lucatello and Malfatti, who studied 11 cases of pellagra with the idea of determining the

quantity of *urea excreted*,—making in every instance from 7 to 11 separate analyses—and finding that the *amount of this substance varied from 10.41—19.51 grams;* in 3 cases there was *diminution of the total nitrogen as compared with that derived from uric acid.*

In 1905 Rossi (5) showed in an interesting clinical paper that there is *excessive indicanuria* in pellagrins, and that the amount is greater than in melancholics.

It has been shown quite clearly by Devoto (2) and Lucatello and Melfatti that there is a *decreased capacity* on the part of pellagrins to *assimilate sugar* properly,—this being regarded by these writers as probably an indication of abnormalities in the functionating capacity of the liver. These results have been recently confirmed by Nistico (5), who, employing 21 subjects for his experiments, and found that all had glycosuria when given 2.5 grams of sugar to the kilogram of body weight; a similar result was observed in 5 out of 8 subjects who were given 1.5 grams of sugar to the kilogram of body weight. It may be remarked that as most pellagrins show degenerative changes in the muscles and are capable of but little activity, a decreased capacity to assimilate sugars might quite well be the consequence of these alterations.

In support however of the view that the decreased urea formation and bad assimilation of sugars is of hepatic origin may be mentioned the observation of Zanon, who asserts that on entrance to hospitals pellagrous patients usually show *Ehrlich's' diazo reaction*, though it generally disappears in a short time.

Brugia appears to have been the first to direct attention to the occurrence of *acetone* in the urine of pellagrins, and his observations have been confirmed by Lucatello (2), who has *produced acetonemia* in the victims of this malady by *cutting down the hydrocarbons* in their diet; in one of his experiments it took the patient 14 days to return to a normal condition, notwithstanding the administration of abundant starches and sugars; under similar circumstances Hirschfeld found in one of his diabetics that this only required 5 days. Lucatello assumes, probably with truth, that hydrocarbons are not utilized properly in pellagrins.

Closely associated with the increase of acetone in the urine is the pronounced *ammonuria* to which Moreschi has called attention in adult and Simonini in infantile pellagra. In the author's experience acetonuria, with a corresponding ammonuria, is exceedingly common in pellagra, and may occur quite independently of other marked symptoms. It would appear that it is not simply the consequence of malassimilation of hydrocarbons, but the disease itself seems at times to produce a disturbance of metabolism that sets up a process of this kind; inasmuch as nausea and vomiting and complete distate for food accompany this condition, its relief becomes a very serious matter when it is once well established, and the patient not uncommonly sinks into a coma, from which recovery probably never occurs. Under such circumstances there is an abundant presence of *diacetic* and *beta-oxybutyric acids* in the urine.

According to Carraroli (2) even in an early stage of the disease, while fats and carbohydrates are well absorbed, this is not the case with the proteids,—especially in a maize diet, and as a result there is great loss of salts by the faces. In the later stages these conditions are accentuated with in addition, poor digestion of fats. He found that phosphoric acid and chlorides are greatly decreased in the urine.

It is interesting to note that Lucatello (3) has shown that the *reducing power* of the urine in pellagra is more commonly diminished than increased, though this difference is not so marked as to be of any importance from a diagnostic standpoint: in one-third of the cases this properly is normal.

D'Ormea (2), in 1905, showed that complete *elimination of methylene blue* is even more rapid in pellagrins than in normal individuals, the average time at which the substance ceases to appear in the urine in the former being 68 and the latter 100 hours. These results have been confirmed and extended by Camurri, who tested the functionating power of the kidney by injecting into the gluteal muscle 5 centigrammes of methylene blue dissolved in 1 c.c. of sterile water. Inasmuch as some of the methylene blue is transformed into a colorless chromogen, and since this substance appears in the urine before the methylene blue itself, this investigator tested for the compound by adding to the urine some acetic acid and boiling, following which the characteristic color of the methylene blue appears

in case the chromogen is present. Where only a small amount of methylene blue occurs in the urine, Camurri recommends that it be abstracted by shaking with one-tenth of its volume of chloroform, evaporating the latter, and redissolving in a small amount of water. As a rule elimination of the coloring material begins in normal individuals in from one-half to one hour; in old pellagrins this period may be somewhat prolonged, but as a rule there is little difference in the earlier periods of the disease. In pellagrins the period of maximum intensity of elimination seems irregular, and may be prolonged to as much as forty hours.

The first attempt at complete studies of the metabolism in pellagra appears to have been that of Brugnola, though his results are unfortunately vitiated by the fact that he examined only 3 patients, 2 of them being under observation 6 days and one for only 5 days. This investigator worked out extensive tables as the result of his observations on all of the excreta, and concludes that *pellagra produces a state perfectly typical of those morbid conditions where there is nitrogen hunger.* He shows that the *assimilation in pellagrins is superior to the normal,* and this he regards as being evidence of a great need on the part of the body for nutritive elements.

Camurri (1, 3) has likewise examined the urine most carefully for the purpose of determining errors in metabolism that might be indicated in this way; inasmuch as the paper on this subject is the most careful and complete heretofore published, it has been thought advisable to include a short résumè of his more important findings.

The *urinary acidity* has been found greatly diminished as the result of a number of analyses made by the method of Freund; unfortunately however this method has been shown by Folin to be inaccurate, and for this reason before Camurri's conclusions can be accepted without reserve this subject will have to be again gone over carefully.

He agrees with Lucatello as to the *variability of the reducing power* of the urine, and finds that the *Ehrlich diazo reaction* is positive only in the graver forms of the intoxication.

Indican was found in considerable quantities where the bowels were constipated, or there was diffuse diarrhoea.

The results were *negative for albumin, sugar, and bile pigment.*

In persons *formerly pellagrous,* but who were apparently well, the *urinary acidity* was likewise *lower than normal,* while the *reducing power* was generally *increased;* the *Ehrlich reaction was negative* and the *indican varied* as in the normal.

This writer then took up the investigation of the metabolism as indicated both by the urine and faeces. He experimented with three types of individuals, namely,

(1) Those who were normal.

(2) Those who had formerly had pellagra.

(3) Those who were in the active stages of the disease.

With each of these groups he used at times a mixed diet, and at others one in which maize largely predominated.

Old pellagrins.—By comparison with normal individuals it was found that those *previously pellagrous* showed a moderate *decrease* in the *elimination of uric acid and ammonia* in the urine. The proportion between the total nitrogenous output and that derived from urea is likewise diminished to a certain extent.

On a *mixed diet* there was but little difference between the normal individual and the old pellagrin respecting the output in the *faeces* of *nitrogen, fats and salts;* on the other hand, where the dietary consisted *largely of maize,* there was a decided increase in the amount of these substances passed both in the normal individual and in the former pellagrin; it is noteworthy that in every instance they were *less in the pellagrous than in the normal individual.* There was likewise in these cases a slight *decrease in uric acid,* while on the other hand the quantity of *ammonia was equal in the two cases.* The proportion between the total nitrogen output from the urine and that derived from the urea was again in this case less than in the normal.

In the *old pellagrin* with *mixed alimentation* the amount of nitrogen and fats eliminated with the faeces was only slightly greater than in the normal person; on the other hand the *amount of salts was nearly a third greater.*

In the old pellagrin placed on a *maize diet* the nitrogen, fats and salts passed from the bowel differed but little from the normal in case the patient was free of diarrhoea, but where the bowels moved often the quantity was somewhat increased.

The *phenols* and *mucin* in the faeces of pellagrins are present only in traces.

In patients *formerly pellagrous,* with a *mixed diet* the *acid reaction* of the *urine* was but little diminished, while the *total phosphates were eliminated in considerably greater amounts than normal.* The same was true of *lime salts.* On the other hand *sodium and potassium and magnesium,* as well as the *total sulphates* and *chlorides* were eliminated in *slightly inferior quantities.*

Where the individual was placed on a *prevailing maize* diet the *acidity is less* and the *total phosphates pass out in amounts inferior* to that observed in the normal urine; the earthy *phosphates* are much *decreased,* while the *alkaline phosphates* are *increased. Lime, soda* and *magnesia* come away in *less* amounts, while the *potash* is *increased.* The *total sulphates* and the *sulpho-conjugates* are passed in *greater quantity* than is the case in individuals living on an ordinary mixed diet.

Active pellagrins.—In *pellagrins who are diseased at the time,* and who are subsisting on a *mixed diet,* the *acidity of the urine is reduced to a minimum.* The *total phosphates* both alkaline and earthy are *decreased* not only as compared with the elimination of normal people living on a similar diet, but likewise with that of normal individuals on a prevailing maize diet, or former pellagrins on either diet. The *calcium elimination* is *normal,* while that of *magnesium is reduced* to the smallest figures as compared with normal persons or former pellagrins on a mixed or maize diet. There is likewise slight *diminution of sodium* with a considerable *decrease in potassium.* There is a *relative diminution* of the *ethereal sulphates* and *slight diminution* of the *sulpho-conjugates* as compared with normal persons on either diet. The *elimination of chlorides is greater* than in normal subjects on any diet, or of former pellagrins on a maize diet.

Where the subject is placed on a *maize diet* during the *active stages of the disease* the *urinary acidity, total phosphates* and *earthy phosphates* are *slightly diminished* as compared with active pellagrins on a mixed food. The *alkaline phosphates* are *slightly increased. Calcium, magnesium, sodium* and *potassium* are *eliminated in slightly increased* amounts as compared with pellagrins on a mixed diet. The elimination of *total sulphates* and of *sulpho-conjugates* and of the *chlorides* is *slightly superior* to that of normal pellagrins on a mixed diet.

Camurri lays great stress in summing up the results of his work on the *low acidity of the urine* as calculated in phosphoric acid (P_2O_5), which means a diminution in the earthy phosphates. He asserts that had he studied more cases, and had the results confirmed those recorded in this monograph, he would have no hesitation in saying:

"The individual who, having been placed under the conditions where endemic pellagra occurs, and who for a certain period of time (6 to 10 days) has subsisted either on a mixed diet or one consisting largely of maize, and whose average acid elimination is not greater than from 300 to 500—equaling 300 to 500 milligrammes of phosphates calculated as phosphoric oxide—is a pellagrin."

The *low acidity,* if taken in connection with the *increased output of chlorides,* becomes of much importance, and indeed that writer is inclined to think that the combination is characteristics of the disease.

Finally it may be mentioned that Camurri is of the opinion that pellagra is *essentially a mineral diathesis,* and that the pellagrin is not one who is suffering from a want of nitrogen, but that his *body has been demineralised.*

Somewhat more recently Nicolaidi and Guillo have reported the results of the investigation undertaken by them to determine the alimentary balances in pellagra.

For the purpose of comparison they administered a dietary principally of maize to a number of normal people and pellagrins. The ration each day was

carefully weighed and analyzed, and the total output of the urine and faeces was subjected to chemical analysis.

It was found that in normal persons there is a gain as regards all of the aliments ingested, with the exception of a slight decrease in magnesia and lime.

On the other hand in those who had been *formerly pellagrous* there was *slight loss of salts*, as shown by an increased elimination of phosphoric acid, magnesia, lime, soda and chlorine; at the same time there was a *lessened output* of *nitrogen* and *potassium*.

The alimentary balance in individuals with *active pellagra* is not observed, there being a *radical and enormous loss in all the nourishing principles contained in the food;* in one instance the difference between the intake and output of nitrogen was 54.28%, of phosphoric acid 96.77%, of magnesia 171.25%, and of lime 431.14%.

While these writers admit that similar losses may occur in other pathological states, they urge that this mainly occurs in the urine, while in the *present instance the increased waste was confined largely to the stools.* The value of this work is more or less vitiated by the fact that it is acknowledged that persons formerly pellagrous may show much the same altered metabolism, and that it may even occur in normal individuals.

Likewise Myers and Fine have made some investigations in connection with the metabolism of pellagrins in South Carolina, which are especially interesting inasmuch as this is the first work of the kind to be carried out in this country. These observers confined themselves largely to an investigation of the protein metabolism, as indicated by the various nitrogenous urinary constituents, and it was found by them that while there is *slight evidence of decreased metabolic activity*—as shown by a decrease of uric acid and creatinine—on the whole there is no *marked variation from the normal.* Creatine was frequently present.

The presence in the *faeces of phenol, indol, and especially skatol in large amounts,* together with *high ethereal sulphates* and *excessive quantities of indican in the urine,* point to an unusual development of bacteria in the intestines.

This subject would not be complete without calling attention to a series of observations that have been made by a number of investigators on the presence of *phenol* in the *urine* of pellagrins.

In the first of his now classic papers on the poisons produced in maize by moulds Gosio (1) called attention to the frequency of the occurrence in bad maize of a substance that gives a *blue color with ferric chloride,* this reaction presumably resulting from the presence of phenols.

Subsequently the *ferric chloride test was found positive in the urine of pellagrins* by Rizzi. Somewhat later this matter was further investigated by Gosio (5, 6) alone and in connection with Paladino, and the following method was recommended for carrying out this test where the quantities in the urine are not sufficient to give a reaction without previous manipulation.

The directions are as follows: As soon as the urine is passed 100 cubic centimetres are evaporated on a water-bath to 15 or 20 c.c., and this is then acidulated with a dilute solution of phosphoric acid and the mixture extracted with ether; the ether is separated, washed several times with water, and evaporated. The residue is then tested in a porcelain dish with ferric chloride, 1 or 2 drops of a dilute solution of this substance being used. Where the ethereal residue contains so much fat that it interferes with the reaction the residue is taken up with a few c.c. of boiling water, filtered, and the test made with the filtrate.

While according to Gosio and Paladino this test is almost uniformly positive in pellagrins, it is unfortunately likewise frequently observed in the urine of healthy people, and cannot therefore be regarded as of any great value in the diagnosis of pellagra.

It is quite evident that the reaction just referred to has no direct relationship with decomposing maize,—at least where this change occurs before the grain is eaten. That this cereal may, however, give rise rapidly in the intestines to an abnormal amount of phenol derivatives seems borne out by the investigations of Brugnola, who found that the *phenols are increased in the urine of pellagrins who are fed on even good maize,* and that there is a corresponding increase in the *toxicity* of this excretion.

Somewhat later Mai and Gatti laid great stress on a series of observations made by them, which indicate that in pellagra there is an increase of both *phenol* and *indican* in the urine, but that the former increases proportionately even more than the latter; as a consequence it is held that the indican and phenol do not combine in the normal way, and that the *latter substance, being in excess, circulates freely in the blood,* with the production of poisonous effects. It is admitted by these writers that this over-production of phenols may also occur in other diseases, particularly in the alcoholic psychoses, but they maintain that it is a *constant and pronounced occurrence in pellagra,* and is of value when taken in connection with other clinical data; these writers confirmed the results of Camurri respecting the *decreased acidity of the urine* in pellagra, but, like this observer, unfortunately operated with Freund's method. More recently Nistico has arrived at the conclusion that there is in pellagra a diminution in the indican when the patient is on a mixed diet.

The same writer says that the urobilin "does not figure in the urine of pellagrins."

In a series of four cases Preti has recently found no noteworthy deviation from the normal in the respiratory metabolism of pellagrins during the acute states of the malady.

In conclusion it is interesting to observe that Zilocchi (1) has called attention to the fact that inasmuch as the caudate nucleus has been shown by him to be involved in pellagra, and as there are centers in this structure that preside over metabolism, the inference is natural that disturbances in the chemistry of the body are almost certain to occur as a consequence.

PARAPELLAGRAS.

(*Pseudo-pellagra*: *sporadit pellagra*: *pellagra of the insane*).

For more than half a century the subject of pellagra, already intricate enough in all conscience, has been further complicated by certain writers either strenuously advocating the opinion that while pellagra is a malady *per se,* it occurs everywhere, and that it has no connection with maize, or that it is not a distinct affection, and is merely a symptom-complex produced by a variety of causes.

Under the leadership of Landouzy (1, 2), Billod (1, 2) and Bouchard (1, 2) these views were clamorously insisted upon something like half a century ago, but as it was shown that many of their so-called cases of sporadic pellagra were really something else, and as doubt was even eventually cast upon all of their observations, the idea ceased to be advocated to any extent, and remained in a state of innocuous desuetude up to some ten years ago, when it again blossomed forth under the leadership of Sambon. Notwithstanding the attention which the subject has received, nothing has been done, particularly by those entertaining such opinions, to determine clearly and definitely that these forms of so-called pellagra are absolutely identical with the endemic type of the malady. Certainly the burden of proof lies on those who maintain the identity of all of these various pathologic states. There even appears to have been a complete lack of a recognition of the fact that the assertion, to be of any value, must rest on uncontrovertible evidence. Our least demand should be that these writers should give descriptions of clinical manifestations such as would enable us to form an intelligent opinion as to the true character of the cases under discussion. But who has done this? Who has even in a single instance in his protocol of the skin findings shown

that he has taken the trouble to inform himself as to the finer points in the diagnosis of the pellagraderms? Notwithstanding the fact, as already mentioned, that many of these alleged instances of this disease have been clearly shown to be something else, there still remain a small number of cases which, if we may rely upon the observations of those reporting them, very closely indeed resemble endemic pellagra; true it is that under such circumstances the description of symptoms is never complete, and there is almost invariably some unusual and bizarre element entering into the case that makes us at once suspicious as to its real character, but which is not of such importance as to show beyond doubt that an error in diagnosis had been made. As a result of this state of affairs we are left uncertain as to what symptoms may or may not develop in the course of true pellagra, and find ourselves confronted with a not inconsiderable contingent of the medical profession which denies the relationship of maize to this disease,—though it should never be forgotten that the advocates of the identity of the endemic and sporadic forms of the affection appear to have been usually actuated in their writings by a desire to upset the accepted views as to the causation of the former. Likewise, the general tendency to regard all patients as being pellagrous who present certain symptoms, and the misleading findings on mocroscopic examination of their tissues where errors in diagnosis have occurred as a consequence, have naturally resulted in the utmost confusion in our studies in the morbid histology of this disease,—studies only through which it appears possible for us to settle definitely the whole pellagra problem. It is therefore clear that a more unfortunate state of affairs could hardly exist, and it must be admitted that it is not wholly the fault of the believers in sporadic pellagra, but has resulted in a measure from the fact that the students of the endemic malady have not pushed more fully and thoroughly their investigations into this matter; on the other hand it is true that the advocates of sporadic pellagra have quite generally, to all intents and purposes, contended themselves with loudly proclaiming that they and they only could be right, while doing nothing to justify their peculiar views. It may, however, be said that beyond doubt those best entitled to an opinion on this subject, either as a consequence of experience or study, have generally held that there is no such disease as sporadic pellagra.

While more than one volume of considerable size has been written on the pseudo-pellagras, it does not appear to the author that the matter is of such inherent importance as would justify a very extensive consideration in the present treatise, and he will consequently content himself with merely calling attention to a few undisputed facts, and to referring to a number of the more popular theories concerning the so-called sporadic forms of the malady.

In view of the fact that this question has not been definitely settled, it has occurred to the author that the terms usually employed to designate these so-called sporadic or pseudo-pellagras are rather clumsy, and are in every instance based on the presumption that we understand the matter more thoroughly than is really the case. Roussel

has classified conditions of this kind as "pseudo-pellagra,"—a term asserting what is really not definitely known; Landouzy and others have referred to a certain type of this pathologic state as "sporadic pellagra," and Billod speaks of the "pellagra of the insane,"—in both of which cases it is unwarrantably assumed that the disease is pellagra. Somewhat less lengthy, and certainly non-committal, is the term "parapellagra," which would seem to fit the exigencies of the situation at least tentatively, and which will therefore be employed in this volume in referring to these various conditions, which, if not pellagra, at least resemble this disease to a certain extent.

The parapellagras may be divided into at least four different groups, (1) alcoholic, (2) those associated with physiologic misery, (3) the pellagra of the insane, and (4) a class of cases to which the term pellagra has been loosely applied, but which are evidently conditions of an entirely alien character, in which skin or digestive disturbances occur; these will now be considered in the order named:

Alcoholic parapellagra.—It is commonly believed by competent pellagrologists that the long-continued use of alcohol sometimes leads to the occurrence of lesions on the hands and occasionally on the face which somewhat resemble those of pellagra. In recent years Leudet, and Bas have reported cases in France, and in Italy Fiorani has recorded a case where a man, who was a drinker, presented all the classic symptoms of pellagra,—even showing the blood picture. Zanon (4) has recently given some statistics on the subject, and records that of 676 pellagrins, in Italy, 57.7% were intemperate. He says where much alcohol is drunk the men with pellagra exceed the women in number. As to whether or not, however, such a result be possible from the affects of alcohol alone there is some dispute, it being held, for example, by Merk (3) that ethylic alcohol alone is incapable of producing pellagroid skin lesions. As bearing in the other direction it may be mentioned that Lombroso (5) believes that most, if not all, of the cases of alleged pellagra in Spain a half century ago were of alcoholic origin, an opinion fully concurred in by Calmarza, who is the foremost modern writer on this subject in that country. Sanz has also adopted this view. On the other hand it seems highly probable that alcohol, owing to its unquestioned deleterious action on the tissues, may not unlikely bring into being any latent tendency to skin lesions that may have previously existed—particularly in those who are debilitated. Thus it would seem that the excessive use of alcohol not unlikely materially augments the tendency to skin eruptions which we know are not uncommon in the badly nourished, and, as Lombroso points out, misery itself is likely to be increased under such circumstances by the subject buying alcoholic drinks instead of food with the little money that comes into his hands. Similarly it seems highly probable that the excessive use of wine not unlikely conduces to the early development of genuine pellagraderms, and we know from the investigation of Daneo and others that the victims of this malady, with their lowered vitality and abnormal nervous state, frequently become subjects of the alcoholic habit. In like manner also the deleterious action of alcohol on the tissues materially aids in bringing out skin lesions in the earliest stages of the insanities, in paralytics, and in those who have developed sclerotic changes in their central nervous systems.

Fortunately, in instances where there is a possibility of alcoholic erythemas, the *history* would in most cases probably at once settle the diagnosis.

Where doubt exists, however, we should attempt to determine as to whether the patient has shown during the preceding years the typical minor manifestations that occur in pellagra, but it should not be lost sight of that more or less similar symptoms have been observed by Lombroso in the beginning of pellagroid attacks where the etiologic relationship of alcohol was clear; under such circumstances he even found that *desquamation of the hands* and *erythema of the arms* occurred, preceded by *headache, vertigo, tremors, epileptiform symptoms, optical illusions,*

weakness in the legs, and *diarrhoea.* However closely these manifestations may resemble those of pellagra—and that there is a striking resemblance it cannot be denied—the two diseases may be probably always differentiated by *going carefully into the history, thoroughly examining the skin,* and *studying the other manifestations.*

On the request of Vedrani, the eminent Bolognese dermatologist Majocchi (4), who is probably the greatest of all authorities on this subject, has indicated in the following terms his views as to the principal differential points between the erythemas of pellagra and alcoholism.

(a) "In alcoholism there never occurs a true pellagrous glove; frequently the lesions is limited to one hand: occasionally it extends to the forearm or arm—but the skin alterations lack the sharp limitation of the pellagraderms."

(b) "They last longer and become pigmented much later."

(c) "The so-called 'pellagrous necktie' does not occur even where a pellagra-like mask is present, and the latter is much more marked on the nose and on the cheeks, giving almost a rosaceous or telangiatoid appearance."

(d) "It is not so likely to come on periodically as the true pellagra, as it may occur at any season."

In addition it may be said that in the *alcoholic lesion the skin is rougher* and the *exfoliation occurs in the form of large lamellae,* which have a *dirty, ashy appearance.* It is likewise true that *fissures do not occur* in the true skin in this affection.

It may be further stated that in the alcoholic parapellagras we are likely to have a *tremor* that begins in the hands and passes quickly to the arms and lips, and that *speech* is *embarrassed* and *hesitating.* Furthermore the *weakness* in this condition *manifests itself first in the upper extremities,* and there are *disorders of coördination,* producing a *staggering gait* and *imperfect prehension,* frequently associated with *cramps.* These patients also exhibit profound *alterations in sensibility,* manifested by tingling in the hands and feet, hyperaesthesia and anaesthesia.

Digestive symptoms are marked in both diseases, there being *anorexia, dysphagia* and *pyrosis,* but in alcoholics the dyspepsia manifests itself in *morning vomiting.* It is noteworthy that we do not have in this condition the excoriations of the mucous membranes of the mouth, and the abundant flow of salty saliva that is so frequent in pellagra.

In *both disorders mental changes are common;* those of *alcoholics are characterized by sombreness, preöccupation,* and a *defiant attitude,* while in the *pellagrous psychoses* there are *mutism, sadness,* and *profound depression.*

In *both conditions loss of strength, vertigo* and *disturbances* of the *special senses* are common.

As both diseases progress the phenomena observed more closely approach each other; anatomic alterations in the viscera occur, accompanied by organic lesions of the intestines, kidneys, heart, liver, and brain, though the changes in the nerve centers are much more profound in pellagra than in alcoholism. As a *fatal termination is approached the two conditions occasionally become in every way identical,* both presenting terminal *diarrhoeas, imbecility, dementia,* and finally *death.*

To this group of the pellagroid diseases evidently belong those curious instances where *drugs produce erythemas* that in some cases quite closely simulate those caused by pellagra; of particular interest are the cases recently reported by Thomas, who in a number of instances observed an erythema—in every way resembling that so commonly seen in pellagra,—on the backs of the hands in patients following the use of sulphonal,—1.2 gm. being sufficient to produce this effect in some cases.

Parapellagra of physiologic misery.—Under this caption may be included a great variety of parapellagras, with the most varied causation and clinical manifestations, and having only in common the fact that they *present usually in the spring, either a dermatitis or diarrhoea alone,* or *the two in combination.* Although cases of this kind have been reported by Strambio, Gintrac, and others,

Bouchard regarded the case described by Roussel in 1839 as being the first undoubted example of what he called "sporadic pellagra," notwithstanding the fact that the latter author at a later time cast doubt on the correctness of the diagnosis. Somewhat later, and particularly during the decade between 1858 and 1868, many cases of this kind were reported, and books were written on the subject by Bouchard (1, 2) and Landouzy (1, 2). More recently cases have been reported by Behier, Aubertin and Brocard, and Dornig.

Bouchard and Landouzy, however, differed in their views, in that while the latter asserted that the sporadic and endemic forms of the disease are essentially the same, and that they are produced by a common cause, he did not deny that the malady is *sui generis*. On the other hand Bouchard maintained that while both varieties of the affection are identical, they represent nothing more than a *symptom-complex*, and are to be regarded as manifestations of various causes, producing symptoms alike in all essential particulars. At a later time this opinion has been concurred in by Winternitz, Carmac, Cecconi, and others.

At this point it is pertinent to point out that with the possible exception of Winternitz, none of these writers have had anything like an intimate acquaintance with endemic pellagra; Bouchard and Landouzy were Frenchmen living where the affection did not prevail, and must have gotten their ideas largely from a study of the reports from Italy, and those part of France where pellagra occurred; Carmao and Cecconi's monographs were nothing more than theses written at the time of graduation, and could not therefore possibly have been the result of opinions formed from experience.

As to just what malady or maladies were chiefly responsible in the past for the majority of cases of this group of parapellagras the records are too faulty to indicate; unfortunately for a more thorough exposition of the looseness that has prevailed in this particular the limits of this volume will not permit the citing of a number of what might be called representative cases of the kind, and we shall therefore have to be content with merely asserting that the published records of these cases are marvels of brevity and inexactness; in many instances the histories are comprised within two or three lines, and contain no further information than that the patient was ill, that he had a diarrhoea, or some sort of skin eruption, or both, and that the reporter had no sort of doubt as to the correctness of his diagnosis. Even in those instances where the clinical details were stated more at length we arise from their perusal with but little more information than we possessed before, as in no single instance examined by the author has the description of the skin lesions been of sufficient accuracy to permit of a judgment as to whether the case was pellagrous or otherwise. Equally faulty are the recorded details of the other symptoms, and after a careful study the best that can be said is that there is a bare possibility that some of the cases may have been pellagrous, though a strong doubt is usually cast on this supposition by the mention of some bizarre or unusual detail which at once leads us to doubt the correctness of the diagnosis. Of course the author does not make the claim that he has thoroughly gone over every case of sporadic pellagra that has been reported, but he has taken the pains to study the 42 examples of the disease reported by Landouzy, and has read with some care the clinical details of all other cases where the reports were obtainable, and feels therefore that he is in a position to say that the great bulk of the material on this subject published in the past is wholly unavailable for assisting in solving this most complex problem.

While, as just remarked, we are not in a position to decide definitely as to the true nature of the majority of cases that have been reported as sporadic pellagra, it may be said without fear of contradiction that a considerable proportion of them are made up of individuals who undoubtedly suffered from cachectic conditions, which in turn were the consequence of serious disorders of one or more of the vital organs. Thus it has occurred not uncommonly that on post-morten these patients were found to have been the subjects of some form of tuberculosis, that they were the victim of cancerous processes, and that even in some cases Landouzy clearly mistook inflammatory conditions of the brain or even typhoid fever for this disease. It is especially noteworthy that many of these cases of parapellagra show symptoms of insanity very quickly after the first manifestations occur—while in true pellagra the patient develops mental disease only after years of deterioration in general health, associated with the minor and major symptoms

of this affection; nor do the descriptions of the mental changes correspond with the peculiar state which we would have a right to expect under the circumstances. Such cases may perhaps after all belong rather in the category of the so-called "pellagra of the insane."

While cases of this kind have been not uncommonly associated by clinicians with inanition it appears almost certain, as is the case in endemic pellagra, that such influences can only act as predisposing causes in the production of the pellagroid symptoms.

Lastly it should be mentioned that from the time that the first case of the kind was reported by Careno in 1794, clinicians interested in this subject have frequently observed instances of so-called sporadic pellagra among beggars and the inmates of almshouses, but, as such persons are not at all infrequently the subjects of serious internal disorders, it is not possible in the present state of knowledge to determine as to whether their diarrhoeas and skin eruptions were the consequences of disease or simply of starvation. In this connection we should not fail to note that a great many of the cases of reported parapellagra were *unquestionably examples of sunburn, vitiligo, erythema exudativum multiforme,* or of *parasitic diseases.*

After what has been said the reader would hardly expect an attempt to define clinically the curious and incongruous assortment of different diseases which have been together reported as pellagra. In addition to the *erythema* or *diarrhoea* the symptoms presented naturally depend upon the nature of the underlying disease. We can only say that the patients have as a rule *shown marked evidences of cachexia,* and that they have developed *erythemas* sometimes of the hands, sometimes of the face, and sometimes of other parts of the body, but as to the exact clinical characteristics presented by these skin changes we can lay down no rule, as they too have necessarily greatly varied. In this connection it can only be affirmed with certainty that quite frequently the skin lesions have been *atypically localized.*

Quite a number of these cases have shown *changes in the mouth,* but here again a lack of detail makes the fact of but little importance. We do not know as to whether these cases commonly present the peculiar lividity of the gums, buccal mucous membrane, and throat, and the lobulation of the upper surface of the tongue, which either alone or together are so characteristic of true pellagra. While Landouzy (1) has particularly called attention to the deep furrows on the tongue as being a common symptom in so-called sporadic pellagra, he unfortunately failed to make the clinical records of his cases correspond with the assertion, as a careful examination of the 25 cases reported by him personally shows mention made of this symptom in only one instance.

In conclusion the author would especially urge upon clinicians the necessity of making such records of their cases as will permit a reasonable judgment to be formed as to whether they are or are not dealing with true pellagra, and it is to be hoped that future observers, instead of unfounded but vehement assertion and long-winded polemics, may devote more time to really learning what pellagra is, and to trying to determine what differences there may or may not be between this affection and the parapellagras.

Parapellagra of the insane.—By far the most common of the different varieties of parapellagra are those that have been heretofore known as the "pellagra of the insane." As is shown by the records of asylums in all parts of the world and the every-day experience of alienists, *dermal alterations are exceedingly common in the insane,* making their appearance on the hands, face, feet, and other parts of the bodies of patients suffering from all forms of insanity; ascribing, perhaps usually with truth, such occurrences to sunburn, cachectic conditions, and parasitic disease, no particular attention was paid to the matter among the earliest students of mental diseases,—the suggestion having come first from Baillarger (1), in 1847, who observed that it was not very rare in sanatoria to see a pellagroid erythema develop on the hands of the insane, even though they had never shown any evidence of pellagra before their admission. In 1852 three cases were published by Cazenave, the younger, and two years later two cases were reported by Merier, but it was not until 1855 that the idea fully

took form following the publication of the writings of Billod. This author was the originator of the view that insanity may *actually produce* pellagra. For the next 10 or 12 years a great number of cases of this kind were reported, and in 1865 there appeared a volume of more than 600 pages by Billod (2) devoted entirely to this subject. In this monumental contribution to this phase of the pellagra problem the author has collected in all 638 examples of this symptom-complex, 136 of which were reported from the asylum over which he presided at Sainte-Gemmes. Unfortunately, however, it cannot be said that anything more was proved than that the insane often exhibit skin eruptions,—a fact which was already well-known. Even a cursory examination of the records of these cases—and they are all included in this volume—shows at once that the *descriptions given are of such character as would in no single instance justify the assertion that the conditions referred to were really of a pellagrous nature.* In a great majority of instances the histories are vague and very brief. Indeed we may say that if Landouzy and his collaborators showed exceptional talent for brevity, that this capacity was developed in Billod to a degree that can only be characterized as genius. As an example of the truth of this assertion may be mentioned that in his records of observations 36 to 55, inclusive, which were reported by this writer from this sanatorium at Sainte-Gemmes, in no single instance was there given anything more than the name, birth place, and address of the patients! While it is true that he observes that he possesses more complete clinical data concerning these cases, it seems rather extraordinary that he should have gone to the trouble of giving their names, birth places, and addresses, and that nothing whatever should be said of their symptoms—especially as his volume was written with the avowed purpose of showing beyond question that true pellagra existed among the insane in regions where maize was not eaten. A careful examination of this volume indicates moreover that it is scarcely unfair to regard the data just referred to as being quite typical of the reports given in other parts of the book; indeed, had the author only said that he had records of 638 cases of insane persons who had never eaten maize, and who presented at some time or other skin lesions of some sort, or that they had diarrhoea or both of these symptoms combined, he would have conveyed quite as much information as can be gained by a perusal of his records from beginning to end.

It is not the intention of the author to try the patience of the reader with an extended review of this remarkable volume, but that he may get some idea of the nature of the cases of "pellagra" which are reported in it, it has been thought advisable to copy word for word a few of the histories selected at random from various parts of the volume—a procedure which fortunately will entail little loss of time in the perusal.

Second observation. R . . . , Jean-Louis, admitted to Maréville 8th October, 1855. Has symptoms of mania following dementia paralytica. Characteristic symptoms of pellagra in 1858. Died 6th April, 1859.

There then follows the records of the post-mortem, which show nothing of any importance except that the heart was dilated and that the liver was very large.

8th observation (Sainte-Gemmes). René L . . . , born at Brion (Maine-et-Loire).

In 1855 a fresh attack of erythema, but of slight degree. Digestive troubles of short duration.

1859 no erythema, health moderate.

1860 in the summer erythema followed by exfoliation on the backs of the hands, without disturbance of general health.

1861 no erythema, health good.

1862 nothing particular. Prolonged remission.

1863 ditto.

16th observation (Sainte-Gemmes). F. R. . . . , born at Puiset-Doré (Maine-et-Loire), living at Varenne in the same department.

1858 the symptoms of pellagra were not reproduced (no preceding record!). In June the patient was taken with congestion of the lungs and died on the 28th.

Autopsy by M. Aubert, the resident physician, did not show cause of death, and nothing particular that could be connected with pellagra.

A further study of the records of this book is surely unnecessary.

Since the time of Billod writers have occasionally reported cases of pellagra in the insane, among whom were Marty, Carmao, Cecconi and others. The most recent collection of cases with which the author is acquainted are those by the writers last referred to. In 1902 Carmao reported 7 cases, with post-mortems in all, and microscopic examinations of the central nervous system in 6, and a year later later Cecconi published the records in 30 cases, a part of which were his own, and the remainder collected from the literature. While it cannot be denied that the clinical histories of these cases are superior to those published by Billod, it is unfortunately the case that they exhibit throughout the same lack of appreciation of the finer points that must be taken into consideration when an attempt is being made clearly to determine as to whether a given case is pellagrous or otherwise, and that after a careful perusal of the works of these authors we are no nearer a solution of this problem than before. It is particularly noteworthy that the post-mortem results and miscroscopic examinations of the central nervous system as given in the brochure of Carmao are by far the most thorough and complete that have as yet appeared in this connection, and *while lesions were quite uniformly found in the brain and cord, they showed marked differences from the changes usually observed in pellagra,* and after being studied carefully leave us still more doubtful than before as to the identity of the symptom-complex resembling pellagra that occurs in the insane.

It may be as well to point out that neither Carmao nor Cecconi could have been very familiar with true pellagra, as both the articles referred to were theses written at the time of graduation; furthermore both appear to have been Frenchmen, and it is well-known that the disease has ceased to exist in France.

We should not neglect to make mention of the fact that *Italian alienists of repute appear quite unanimous in the opinion that pellagra is a distinct disease,* and that therefore it is not a symptom-complex, and as a consequence hold that the parapellagras of the insane are quite distinct from the true disease; particularly instructive in this connection are the writings of Garbini, who has reported several cases where the patients presented typical pellagrous symptoms, though evidently suffering from some other disease.

When we come to an examination of the symptomatology of the parapellagras of the insane we are confronted with the same difficulties that we uniformly meet with in considering the entire subject.

As the patients are insane, we have little or no knowledge as to either the physical or mental symptoms that preceded the outbreak of the pellagroid symptoms, nor would we know in the event of our possessing such information as to whether the symptoms arose from an insanity due to other causes, or from a pellagrous state.

As regards the individual symptoms we are almost equally in the dark, as writers have quite uniformly failed to distinguish between the pellagraderms and other lesions of the skin more or less resembling them. As shown by Cramoisy and Pouquet three patients from the asylum at Sainte-Gemmes, who were exhibited by Billod at the Academy of Medicine in Paris as typical examples of pellagra, *were in reality victims of barber's itch.* Later Bazin *not only determined that the supposed pellagrous erythemas at the asylum just mentioned were due to this cause, but he likewise showed that those at Auxerre were of a similar nature.* Neusser (1) mentions that the disease of the skin produced by *favus* has likewise given rise to the same error. There *is no room to doubt furthermore that patients of this kind frequently suffer from sunburn, vitiligo and erythema exudativum multiforme,* all of which may easily give rise to error where careful examinations are not made.

But little is said as a rule by writers on this subject of the gastrointestinal changes. Occasionally they mention that a *diarrhoea* exists during the course of the trouble, and in some instances a *sore mouth* has been noted, *but on the whole lesions of this kind seem much less pronounced* than is the case in typical pellagra.

A knowledge of the psychic states that are supposed to occur in connection with these cases are of such a fragmentary nature that we may be said to know really nothing of the subject.

The only paper that the author has been able to discover which deals with this subject in any way approaching a clear and satisfactory manner is that of Aubert. In 60 cases of pellagra of the insane this writer observed that the trouble was characterized by *melancholy, stupidity,* and finally *dementia;* few were *idiots,* and he *never* saw patients *exhibit agitation.* When *maniacs are attacked by "pellagra"* there is a complete transformation, as a consequence of which the patient develops a *profound melancholy.* In all cases where this disease develops during insanity of any kind the patient exhibits *dullness, feebleness of intelligence* and *volition,* and a very great *repugnance to locomotion;* the patients are always *dull* and *gloomy* and maintain an *obstinate silence* or reply to questions only with difficulty; usually they complain of *no pain.* These *symptoms disappear* with the other pellagrous manifestations, but *recur* during *subsequent outbreaks;* in the *intervals there is a return of the same form of insanity exhibited before the pellagrous symptoms made their appearance.* This writer asserts that *lypomania* and *dementia* are the only forms of delirium which he has observed in these patients; in one instance *religious monomania* developed. Only one patient developed *embarrassment of speech.*

The writer concludes that *profound melancholy* principally characterizes the *altered mental state of persons previously insane who become pellagrous.* He observed in *no instance* a tendency to *homicide or suicide.*

On the whole, however, the utmost confusion exists respecting the mental changes in these cases—it only seeming to be clear that the pellagroid symptoms occur in a variety of different psychoses.

In this connection we cannot do better than quote the works of the committee on public hygiene appointed by the French academy to investigate this subject at the time it was so much discussed in the late 50's of the last century. They say,

"Having examined into the researches of the physician who has reported so many alleged cases of endemic pellagra in the asylums for the insane, we do not consider the matter of sufficient importance to require discussion. Never has it been the case that confusion between different morbid entities was more evident. The last cases in particular that were reported, which exhibited erythemas on the extremities, and cachectic diarrhoeas occurring during the latter stages of depressive forms of insanity, dementia, general paralysis, and lipomanic stupidity, have not the slightest connection with true pellagra."

Under such circumstances it is of course impossible to point out the peculiarities that could be in any way looked upon as being diagnostic. It is however true that a certain proportion of these cases—perhaps the great majority—show skin changes that are doubtless akin to the erythematous conditions that occur in debility and physiological misery—conditions probably due to a combination of general ill health and weakened resistance, senile changes in the skin, arterial disease, and, perhaps more important than all, imperfect innervation. Cases of this kind would likely show a family resemblance, as is evidently thought by Zilocchi (2), who has said that in general the following characteristics distinguish the lesions of endemic pellagra from those of the parapellagras. He says,

"The erythema of pseudo-pellagra is darker than in genuine pellagra, with absence of the underlying redness; the former phenomena disappear more quickly, as do the erythemas from sunburn, and exhibit a greater cutaneous distrophy and a dryer lesion. On the other hand the pellagrous erythema is of a deep rel coloration, which persists for a long time, and the lesion is usually more profound and of a more moist character. Likewise in true pellagra the color of the skin of the body assumes a yellowish aspect not observed in pseudo-pellagra, and it is typical of these cases in the beginning that there are many large commodoes on the nose, which assume a yellowish color."

In conclusion it should be pointed out that this phase of the problem is scarcely nearer solution than it was at the time that Baillarger first called attention to skin eruptions in the insane. Are there cases where the patient has neither hereditary nor acquired pellagra, in which he first becomes insane, often with symptoms of general paralysis, and yet who later develops typical pellagrous legions of the skin and intestinal tract? Unfortunately we cannot answer. We can only say that it seems highly improbable.

Naturally the solution of this phase of the problem rests with the alienist, but in order that he may really supply the information we so much need and

desire he must be absolutely certain that his cases are pellagrous. As we have no means in the present state of knowledge of differentiating with certainty the pellagrous psychoses from those produced by other causes, it would seem that it will be necessary first to study cases where typical pellagra has developed, followed by insanity, in regions where maize enters largely into the dietary. After death these cases should be examined most thoroughly and carefully by capable pathologists, and after a sufficient amount of clinical and post-mortem data have been collected, similar studies should be made of all cases developing pellagroid symptoms where the insanity preceded such manifestations, and these investigations must comprise cases where maize both is and is not commonly eaten. Until such work is faithfully and carefully carried out it is but a waste of effort, time and money to carry on investigations respecting the causation of pellagra, as we could not hope to determine this matter finally and definitely until we are perfectly certain as to what pellagra is and is not.

In conclusion attention may be again directed to the fact, recently reported by Thomas, that pellagroid eruptions often follow the use of sulphonal; as this drug is much used in many asylums for the insane it is not improbable that some of their cases of "pellagra" have been produced in this way.

Cases reported as sporadic pellagra clearly of different character.—From time to time in medical literature cases have been reported as such which were clearly not pellagrous, but at the same time the attendant circumstances seemed to indicate that they could hardly be included within the parapellagrous categories heretofore considered.

Such cases have as a rule shown in their symptomatology such slight resemblance to pellagra that no one acquainted with the disease would have thought for a moment of so considering them; examples of these are two of the cases reported by Careno.

In other instances the patients have suffered from nervous affections; as for example a case recently described by Hammond in which the skin lesion encircled the lips, and in which insanity quickly followed: another case of this character is that reported by Box, where the patient, a lad 8 years of age, after having previously suffered from nystagmus and ataxia, later developed an inflammatory lesion of the skin that, crossing the bridge of the nose, *extended outward around the eyes;* when these symptoms are taken in connection with the fact that this patient's brother suffered in a similar manner, there is no room to doubt that this case had nothing whatever to do with pellagra, and that it probably belonged within that curious clinical group of congenital disease of the central nervous system associated with the name of Fredreich.

Lastly it may be mentioned that it was shown by Costallat (1) that the disease that occurs in some provinces of Spain, known as *flema salada* and *enfermedad del higado,* is in all probability nothing more than a variety of acrodynia produced by decayed wheat.

Cases of supposed pellagra, occurring wholly in beggars, have been reported from Spain; that this trouble is some affection of a parasitic nature, or is a disease produced by malnutrition and filthy habits, associated with skin lesions, seems altogether likely.

CHAPTER V

Diagnosis.

As the author is one of those who is convinced of the close relationship of maize-eating to pellagra, he naturally feels that a history of the former is of the greatest importance in making a diagnosis of the latter. But he does not believe that it is essential that the victim of the malady be himself a consumer of maize, since there can be no doubt whatever that the malady is hereditary, and that it may therefore appear in the offspring of pellagrins even where they have never made use of Indian corn; that such influences are most obvious during childhood cannot be denied, but that they likewise operate no less inexorably in later life seems certain, notwithstanding that it is rarely the case that adults have this disease without having regularly at some time consumed maize products. We are not, however, in a position to assert roundly that maize eating is absolutely essential for the production of the malady, as it is not impossible that persons with an hereditary taint should become pellagrous when the changes incident to advancing years begin to make their appearance, and that the former may be produced, and both conditions accentuated by intoxications the consequence of the consumption of other cereals in which fermentative changes have occurred. That genuine pellagra, however, occurs without an association of maize consumption, either in the person affected, or in his immediate ancestry, the author thinks extremely doubtful, and is indeed inclined to the opinion that such a relationship is essential, though of course the possibility of this view being erroneous is recognized. However, it must be freely admitted that a condition is occasionally encountered in those who deny ever having eaten maize products—particularly in the insane—that superficially bears a marked resemblance to pellagra, and that many capable clinicians have regarded the two conditions as being essentially the same. That many cases of this so-called sporadic pellagra have been found on close examination to be something else entirely is well-known, and that the histories given of the remainder are far from convincing in an overwhelming proportion of cases any capable pellagrologist would declare; the few instances in which the resemblance to true pellagra is really striking have never, so far as the author is aware, received the close clinical and post-mortem examinations that would warrant

the assertion that they were identical with this disease, there having been in no case within his knowledge any attempt at a study of the patient's ancestry, or adequate observations on the skin symptoms, nor have there been complete and thorough examinations of the central nervous system and other internal organs by modern methods after death.

Irrespective of any association with maize, there are few if any facts of a general character that materially bear on a diagnosis of pellagra. It is true that the disease appears never to occur in very young infants, that it is relatively rare in childhood and early manhood, and that it generally makes its appearance during the fourth or fifth decade of life, occurring rather earlier in women than in men. Finally it may appear in old age, though a close examination would undoubtedly have revealed the minor symptoms of the malady at a much earlier period under such circumstances.

It appears to be well established—though this has been denied by some capable observers—that the malady is on the whole somewhat more common in women than in men. Clinicians undoubtedly see the former suffering from this malady more commonly than they do the latter, but this might result from a variety of causes, among which may be mentioned the fact, already referred to, that the disease occurs at a later time in the male than in the female, and as a consequence the women is likely to be seen more often than the man by the general practitioner. It is likewise true that after the disease develops it is apt to attack women with much greater regularity each year, which further accentuates the discrepancy. It is therefore apparent that mortuary statistics would be the only data that would be entirely reliable in this connection. The author also believes that such discrepancies are frequently the result of the minor forms being more common in the male, and that he is therefore not seen so often by the clinician. However, notwithstanding the sources of error referred to, it is generally believed that pellagra occurs in women more frequently than in men,—the proportion being something like five to four.

Race appears to be of no particular importance as a determining factor in the incidence of pellagra, though it has been noted in Italy, Roumania, and in this country that Jews rarely suffer from the malady.

In the old world occupation appears to play a considerable role in the production of the disease, it being largely confined to the farming classes, but this relationship is by no means so close in America,—doubtless as a result of the fact that in the Southern States maize products are a staple diet with all classes, and that farmers frequently remove from the country districts to towns and cities; that a great majority of our pellagrins are, however, dwellers in the rural districts there can be no doubt, and that this is the result of their being almost universally maize eaters seems all but certain,—the effect being accentuated by the hardships and exposures incident to tilling the soil, the poor food, the monotony of their lives, and the often unhygienic surroundings, all uniting to bring about premature senility.

Pellagra is, however, by no means confined to the poor and to the agriculturists in the southern part of the United States, as it is observed with very great frequency among well-to-do and even wealthy people,—this corresponding strictly with their maize eating habits, and contrasting sharply with the rarity of the disease among the higher classes in the old world, where the wealthy practically eat no maize.

As the author has attempted to make clear in dealing with the symptomatology of this affection, he feels no doubt whatever that an outbreak of the external and major pellagrous phenomena is always preceded by a greater or less number of years during which the patient is not entirely normal, and that he suffers from certain minor disturbances that are far more characteristic than the more obvious symptoms upon which the diagnosis of pellagra is ordinarily based. In a paper (3) written some years ago the author particularly directed attention to the great value of these earlier manifestations from a clinical standpoint, and urged their close study as being our only means of arriving at a diagnosis at the only time when the patient can be really benefitted by proper therapeutic measures. The symptoms to which reference is made are really at bottom in the great majority of cases referable to the nervous system, though at times the connection is not obvious.

First and foremost the patient is almost always constipated, and has been so far a number of years when he is first seen by the clinician; occasionally, though this is by no means uniformly true, the constipation alternates with diarrhoea.

As the patient approaches middle life he begins to observe that he suffers from what is called "biliousness," particularly in the spring and early summer, this condition being characterized by malaise, anarexia, headache, coated tongue and foul breath, and a peculiar yellowness of the skin, all of which is more or less relieved by the taking of purgatives. He usually improves in the summer, though occasionally he may have recurrences of these attacks of indigestion and autointoxication even during the hot months, or in the autumn.

With advancing years, the patient sooner or later begins to have attacks of great mental depression in the spring, which are accompanied by an extreme aversion to all forms of exercise, whether physical or mental, and weakness, particularly marked in the legs; along with these symptoms dyspeptic disturbances develop, there being often a peculiar burning in the stomach, pyrosis, fugitive neuralgic pains in the abdomen, to which is added a burning sensation in the exposed parts if the patient labors in the sun. After a few weeks these symptoms subside and the sufferer returns to a fairly normal condition, though he may have recurrences during the summer or autumn. Many patients suffer from symptoms such as have been described for a great number of years before developing external manifestations, *and the author is of the opinion that in the great majority of pellagrins the disease never develops further.*

In a certain proportion of cases the symptoms that have just been described come on with unusual severity in the spring, and the patient

has added to the accustomed manifestations a sore tongue and perhaps a scaliness of the backs of the hands or face, but even under such circumstances a number of such attacks may occur before he develops the frank outspoken symptoms that are generally regarded as diagnostic of this affection, and the author thinks that not uncommonly he may never do so.

In still other cases the time ultimately comes when the patient becomes pellagrous in the ordinary acceptation of the term; the symptoms already mentioned come on with unwonted severity; usually after exposure to the sun, or sometimes after a slight injury to the skin of the backs of either one or both hands, a peculiar livid redness suddenly makes its appearance in these situations, to be quickly followed by the development of inflammatory changes in the oral cavity, and usually diarrhoea. The order in which these symptoms develop is subject to great variation; in the author's experience soreness of the mouth frequently precedes the erythema, and not uncommonly he has observed a diarrhoea ushering in the more severe pellagrous manifestations.

Practically without exception pellagrous patients show marked nervous symptoms, which become accentuated during the attacks just referred to, and which are commonly of a hypochondriacal nature.

It is likewise the case that practically all such patients exhibit certain mental symptoms, the patient being in a state of profound melancholy, and he cannot as a rule be induced to think of anything other than his own condition, which he commonly regards as hopeless. He likewise suffers from loss of memory, and an inability to think in a normal manner. In a small proportion of cases a pronounced mental alienation occurs,—a condition which may exceptionally usher in the major pellagrous symptoms.

We will now consider as briefly as possible the more characteristic peculiarities of the various pellagrous manifestations.

The skin.—It is unquestionably true that the name given this disease, and the striking character of the dermal symptoms have resulted in these manifestations being accorded an undue and wholly unjustifiable prominence in the minds of many who have written on the subject. As a result of this fact a great many mistakes in diagnosis have been made, since, on the one hand, it has been assumed that the disease cannot exist without some such phenomena, and, on the other, that almost any symmetrical, irritative skin lesion, not clearly something else, may be so classed. As before remarked the author has little doubt that it will be ultimately found that pellagra in some localities—particularly in the tropics—is only rarely accompanied by the classic pellagraderms. As a matter of fact, even after the affection is well established, many patients never at any time present such manifestations, and where they occur it is only in the rarest cases that they persist throughout the course of the malady. It is equally true that where such lesions do occur they, if typical, run an extremely characteristic course, and are said by competent dermatologists to be on the whole easily distinguishable from all similar conditions for

which they might be mistaken. It is greatly to be deplored that this has been so little recognized, as ignorance of the fact has given rise to much confusion, and bids fair to continue to do so in the future. It is only the atypical skin lesions of this disease—and they are, unfortunately, fairly common—that give rise to justifiable error; from such manifestations alone it is never permissible to make a diagnosis, —particularly in the insane, among whom more or less similar skin symptoms are very frequent, and in whom it is rarely or never possible to get an accurate history.

Notwithstanding the assertion of some to the contrary attention should be here again directed to the fact that so far as known there are no characteristic histologic changes of the skin in this malady. It is perfectly clear that the pellagraderms are at bottom the result of nervous disturbances, though the alterations that occur in the skin from exposure probably act as predisposing causes,—often in association with thermal or mechanical agencies. One of the most important peculiarities of the pellagraderms is their usual occurrence in the spring, following several weeks of mental and physical depression and ill health of the patient; however, periodicity of the dermal alterations is by no means pathognomonic, as it is known that under certain circumstances more or less similar changes occur in the skin at the same period of the year which could have no connection with this disease.

Sometimes, preceding the ordinary erythema, symmetrical maculae, in the true dermatological sense, appear on the backs of the hands; while ordinarily these spots disappear, in some instances they persist and coalesce with the more typical lesions that later develop; under such circumstances they may show evidence of hyperaemia, and may be raised above the surface to a certain extent.

Nothing is more characteristic of the true and typical pellagraderms than their *very sudden development*—occurring within a few hours, and usually following exposure to the sun; they are at first red, later becoming livid, generally first affect the backs of the hands near the metacarpo-phylangeal articulations, and gradually extend outward on the backs of the fingers to the middle of the second joint, and upward on the wrist, and sometimes on the lower part of the forearm to the point where the surface is covered by the clothing; in some cases the discoloration advances to the ends of the fingers, and may even spread to the palmar surface of the hand,—being under such circumstances generally limited to the skin covering the ball of the thumb; occasionally the erythema extends up the outer surface of the forearm, and may ultimately involve the skin of the arm.

Particularly in those who go barefoot the backs of the feet may be attacked, and the lesion may spread to the anterior surface of the leg; in some instances the erythema is confined wholly to this part of the body, or may occur here first and later develop elsewhere.

Not uncommonly the face is likewise involved, the lesion appearing particularly on the cheeks under the eyes, the bridge of the nose,

and the forehead, and when well developed may constitute the so-called "pellagrous mask."

Less commonly the process extends to the lower portion of the neck, and under such circumstances usually involves the skin covering the sternum to a greater or less extent; when this lesion is well developed it is generally known as "Casal's necktie," owing to the fact that the discoverer of this disease was the first to describe it; in rare cases the lesions may appear on the shoulders, around the genital organs, and in some instances may involve the skin of the entire body.

It is especially noteworthy that the pellagraderms are almost always symmetrical or nearly so.

Wherever the lesion occurs it quickly presents the livid-red appearance to which reference has already been made, and is very frequently acompanied by a burning sensation,—particularly where the patient exposes himself to the sun; this redness is the consequence of hyperaemia, as is shown by the fact that it momentarily disappears on pressure. The skin presents a swollen and rather angry appearance, but little or no pain occurs. The author is in full accord with Strambio, Gemma and others, who assert that itching is not a characteristic symptom of true pellagraderms, and perhaps never occurs in uncomplicated cases.

After a pellagraderm has persisted for a few days careful inspection will reveal minute, angular, grayish scales that first make their appearance at the point where the lesion began, and which gradually follow it outward as it spreads in every direction. In the average case redness persists for from ten days to three weeks, and then gradually subsides, leaving a roughened and scaly surface; the derma now shows a dirty, coffee-colored pigmentation.

In the course of two or three months after the first attack the skin usually returns to a fairly normal condition, though close inspection will show numerous fine lines that give the diseased area the wrinkled appearance seen in old age.

In severe cases a clear, alkaline, sterile fluid may collect under the epiderm, and, pushing it outward, form small blisters scattered over the diseased area; these blebs may burst, leaving raw surfaces over which scabs form, or the fluid may be absorbed. They show no marked tendency to become confluent, except on the neck, where, according to Merk, they may cover the entire diseased surface; for this condition this writer suggests the name of pimphigoid pellagraderm.

It sometimes happens that the blebs become infected, and under such circumstances pustules result.

In some instances where the inflammatory phenomena are exceptionally severe hemorrhages may occur in the tissues,—thus constituting a hemorrhagic pellagraderm.

Occasionally the lesions may take on a more or less chronic course, and the redness and scaling may go on under such circumstances for months.

After several recurrences, or even after a single severe attack, the skin appears thinned after the pigment is absorbed, and may then

present a peculiar clear, grayish, parchment-like appearance, with loss of elasticity; in such areas localized, ecchymotic spots may develop, which result from trauma, often of an exceedingly mild character. It is here that we find histologically a condition closely resembling that which occurs in senility, and which, barring the extreme severity of the pellagrous lesions, is in every way identical with those found in this condition.

In old pellagrins, and particularly in hereditary cases, symmetrical areas of acne, with comedoes, may appear about the face, and in the same situation groups of sebaceous glands may become enlarged and produce small elevated areas on the skin surfaces. As pointed out by Gemmal (9) there sometimes occurs a pellagrous pityriasis.

In some pellagrins likewise small boils may occur in succeeding groups over the trunks and legs. These lesions present a livid appearance, are not painful, though when squeezed a small drop of pus will frequently exude.

It should never be forgotten, as Gemma (8) points out, that in rare cases pellagra gives rise to pemphigus, ichthyosis, or a papular erythema.

In aggravated cases the whole skin may present a more or less pigmented appearance, and, particularly in severe nervous forms of the malady, localized dark-brown areas may appear in various parts of the body, which are not in all cases symmetrical. This discoloration is much more marked than the yellowish hue the skin often assumes in the beginning of pellagrous attacks.

It should also be remembered that deep pigmentation not uncommonly develops on the hands, face, neck, feet and legs following the ordinary pellagraderms; after repeated attacks in some instances the tint becomes very dark, being in rare cases black.

Now and then the skin may assume a marbled appearance, particularly on the legs in women; this condition is brought about by the formation of reddish or violaceous areas of discoloration between which the normal skin appears.

Occasionally actual ulceration may occur. Such lesions present themselves as cracks in the skin, which are most common in those parts of the body where the skin and mucous membrane join.

Edema is occasionally also present.

As particularly pointed out by Gemma (5) onychia of pellagrous origin is occasionally observed, leading to considerable deformities of the nails; he says that these nail diseases are to be differentiated from those of syphilitic origin by ulceration frequently accompanying the latter.

GASTROINTESTINAL SYMPTOMS. — *Mouth.* — Occasionally, in mild forms of the disease, there may be no acute changes in the mouth, though in a great majority of instances such alterations early make their appearance, and continue throughout the course of the attack.

Generally speaking it may be said that these lesions are characterized by a hyperaemia not equibly diffused, but present in

irregular areas, in the midst of which there are many paler zones; there is a general tendency to serous effusion and exfoliation, with inflammatory alterations of the deeper structures that are rarely primitive but are consecutive to the alteration in the epithelial coating. These lesions do not necessarily accompany other intestinal phenomena, and frequently occur where no symptoms referable to the lower part of the tube exist, and may occasionally present themselves as the only major manifestation of the malady; they are never the consequence of an extension from the neighboring skin surfaces, and show no tendency to occur in the distribution of any particular nerve; they are clearly the result of general nervous disturbances, associated with lowered vitality. In several instances the author has seen these manifestations quickly appear after skin lesions that seemed clearly determined by local injuries.

The earliest and most common of the changes in the mouth are those that occur on the tongue, which consist in the beginning of a white coat, rarely uniform in character, and generally appearing as small rounded areas surrounded by more or less normal mucosa. Somewhat later epithelial exfoliation occurs, and, as a consequence, the surface becomes ulcerated and the deeper tissues inflamed, following which the entire surface of the tongue becomes involved; the process, like the skin lesions, is very acute in its beginning but often requires months to heal.

Sometimes these alterations are confined to the tips of the papillae, the lesions consisting in exfoliation of their epithelial coating, or in the formation of minute blebs.

In old pellagrins and in the hereditary forms of the malady there sometimes occurs a peculiar alteration of the epithelial coating, with flattening of the papillae, not accompanied by marked inflammatory changes, and giving to the tongue a smooth, slick, polished and homogeneous appearance. Sometimes combined with it and in the same class of cases there is hypertrophy of the epithelial coat of the papillae. This lesion deserves histologic study.

Not uncommonly the patient's tongue presents the peculiar fissured appearance to which reference has been already made. Whether this condition is principally a consequence of enlargement the result of previous inflammatory attacks, or whether it be an effect of semiparalytic conditions in some of the muscles of the organ cannot be said with certainty, but it is not improbable that it is in a measure the result of both. Whatever may be its origin, there can be no question of its great diagnostic importance, and the author would regard as being likely pellagrous any patient presenting it in whom syphilis could be excluded. It is sometimes necessary to make the patient protrude his tongue and then pass the finger over it before the presence of these fissures can be clearly determined. It should be particularly remembered that they persist in the intervals between the attacks, and have no immediate relation whatever to the acute inflammatory changes. They have been observed by Gemma (4) in children the offspring of pellagrins.

Between the attacks the tongue often appears long and thin, and when the patient attempts to protrude the organ it may curl up, with the result that it cannot be forced out of the mouth; in other instances the edges may be turned up or down, giving the tongue in the first instance a troughed and in the latter more or less of a cap-like appearance. Ultimately the organ becomes very small, and its surface pale,—often more so than the anaemic condition of the patient would warrant.

In very chronic forms whitish or yellowish streaks of cicatricial tissue may be observed beneath the mucous lining, and the tongue quite uniformly acquires the slick appearance to which reference has already been made.

Not uncommonly the organ shows the impress of the teeth at its edges, and it is also slightly tremulous.

Simultaneously with the changes in the tongue similar alterations make their appearance in the corners of the mouth, the lips, the gums, and the buccal mucous membranes, frequently followed by exfoliation of the mucous surface, and the formation of painful ulcers that bleed on being touched.

At the height of the process, when almost the entire mucous covering of the mouth is involved, mastication becomes almost impossible, and owing to an extension of the process to the throat even swallowing may be painful and difficult.

Of extreme interest are the peculiar livid appearances of the mucosa of the lips, gums, buccal mucous membranes, palate and pharynx to which Gemma (4) has called attention. These livid areas are quite constantly found in chronic pellagrins, are symmetrical, and particularly on the palate may show a sharp line of demarcation corresponding to the line of juncture of the hard and soft palate. The lesions are characterized by their peculiar color, which is in marked contrast with the coppery appearance of syphilitic lesions, and the purple tint of those of scurvy. These lesions become more pronounced preceding and during the acute attacks, and, while ordinarily they are not accompanied by inflammatory changes, and are painless, at such times may become the seat of ulcerative processes.

The stomach.—Almost all pellagrins suffer from digestive disturbances, consisting frequently of a burning sensation, pyrosis, an uncomfortable feeling of fullness after meals, gas formation, and more or less pain, all of which become particularly pronounced in the late winter or spring,—an exacerbation of such symptoms usually preceding an ordinary pellagrous onset.

On analysis of the stomach content following test meals the hydrochloric acid is generally found markedly decreased, with a corresponding diminution in the gastric ferments and their zymogens; at late periods of the disease there is usually a complete achylia, with entire absence of ferments, associated with which there is usually a formation of organic acids.

The intestines.—Diarrhoeal conditions are by no means uniformly present during the acute pellagrous attacks, though some disturbances of this kind is extremely common. Occasionally looseness of the bowels may be the first of the major symptoms to develop, but more commonly it follows the changes to which reference has been made.

In the earlier stages there may be some tenesmus, with dysenteric stools, but as a rule where such a phase occurs it quickly gives place to a simple diarrhoea. As a rule the diarrhoea is of moderate intensity, there being from three to six or eight stools in the twenty-four hours, but cases are not wanting in which the disturbance becomes very severe, and under such circumstances is not uncommonly the immediate cause of death.

In the earlier stages the stools may contain mucus and blood, but at a later time they are of a yellowish or greenish appearance, having a foul odor and an alkaline reaction, and are usually extremely thin and watery.

The eggs of intestinal parasites are frequently encountered in the stools of European pellagrins,—hookworm being particularly common, but they are only rarely seen in America.

Nervous symptoms.—Nervous symptoms are exceedingly common in pellagra, which, together with the psychic changes, are regarded by the author is being preeminently the manifestations that distinguish this disease.

In the milder forms of the malady in the male hypochondriacal or hysterical symptoms, a peculiar melancholy, and a constant preöccupation with himself and his symptoms, accompanied by digestive disturbances are frequent, while the femals exhibits distinctive, highly nervous manifestations, associated with vertigo, the globus hystericus, and motor derangements. While these symptoms may accur at all times of the year, they become peculiarly marked in the late winter and spring, and always to a greater or less extent precede the typical attacks, whether they be of a mild or severe character.

The motor symptoms are more particularly referable to the lower limbs, and consist in great weakness, with semi-paralytic conditions, at times associated with extreme spasticity, accompanied by marked loss of faradic irritability, but rarely or never by the reaction of degeneration. In very severe forms of the disease there may be weakness of the sphincters, paralyses of the bladder, and dysphagia.

Such changes are accompanied by alterations in the deep reflexes, there being an increase much more commonly than a diminution. There is also disturbance of the cutaneous reflexes of the lower extremities; the plantar reflex exhibits modifications of intensity in nearly half the cases, and variation in form almost as commonly; the alteration consists in exaggeration, diminution or absence, while the Babinski reflex occurs in a considerable proportion of cases. Associated with these altered reflexes of the legs Neusser has observed the facial phenomenon not uncommonly. The pharyngeal reflex seems to be uniformly normal, while the pupils occasionally show derangements.

Sensory symptoms are also extremely common, consisting mainly in disturbances of the sense of touch, though alterations in the thermal and pain senses may sometimes be detected on careful examination; the muscle sense seems rarely to be disturbed.

The special senses likewise suffer to a certain extent, there being at times disturbances of taste, smell and of hearing. The eyes suffer more or less in about 60 per cent. of the cases, though no characteristic lesions are present. In the main the alterations consist in muscular weakness and opacities of the lens and light-conducting media. It does not appear that the nerve is as a rule affected, though choked disc and amaurosis are not excessively rare.

Mental symptoms.—Mental symptoms of a pronounced character are not uncommon in pellagra, being of sufficient severity in about 4 per cent. of the cases to cause the victims to be placed in sanatoria for the mentally deficient. That the proportion of minor mental disturbances is much greater there can be, however, no doubt. In 1,436 cases of pellagra Grimm found 7.6 per cent. showing psychoses, while Singer says that more or less mental disturbance occurs in about 40 per cent. of all cases.

Grimm found that psychoses are more common in the colored race than in the white,—the percentage being lowest in the white female (6.7 per cent.), and greatest in the colored male (19 per cent.). It is thus seen that psychoses in pellagra are very common, and consequently offer proportionate opportunities for mastakes in diagnosis.

Having but little knowledge of mental diseases, the author scarcely feels in a position, even after a very careful study of all of the available literature on pellagrous insanities, to discuss intelligently the opinions arrived at by others. He can only say that a conscientious effort has been made to bring to the English reader a synopsis of the opinions of all of the principal writers in Italy, France, Austria and Roumania, and to express the hope that he has been fairly successful in catching the many shades of meaning which all must acknowledge is exceedingly difficult where one attempts to translate from foreign tongues the views of experts on an unfamiliar subject. In the pages that follow the author will consequently only attempt to portray for those, who, like himself, have little knowledge of insanity, what appears to be the opinions of the alienists who have written on this subject, and will refer those who are especially interested in this phase of pellagra to the chapter on symptomatology, under the caption of mental diseases.

From a study of these papers it would appear that there is a diversity of opinion as to the characteristics distinguishing the pellagrous psychoses.

Some alienists—and they appear to be in the majority—regard the insanity occurring in this malady as being made up of a group—disjointed and in no way connected—of well recognized psychoses, such as melancholia, mania, general paralysis, amentia, dementia, etc.; they believe that pellagrous patients may present any one of these

well-known types of alienation, or that different forms may succeed each other in the same patient.

On the other hand many very competent observers maintain that the mental change in pellagra really corresponds to only one of the classical types of insanity; thus it is asserted by some that confusional insanity is preëminently a disturbance that distinguishes this disease, while others are equally positive that it is really melancholia,—the latter opinion having been much more common among the earlier writers, and not so frequently maintained since it has been accepted that this psychosis is a phase of what is now called manic-depressive insanity.

Still others believe that pellagrous insanity may be differentiated from all others by certain distinctive pecularities, and that the resemblance of the mental symptoms to well-known types of insanity is deceptive; observers maintaining this view assert that a careful examination of the pellagrous patient will always reveal the fact that his mentality is at least to a considerable degree preserved, as he recognizes the nature and hopeless character of his illness, understands where he is, etc.

This difference of opinion is perhaps after all not so radical as might at first glance appear, since it may be the case, as hinted by one distinguished Italian alienist, that the whole misunderstanding simply arises from a lack of careful and thorough study of these cases—a view which it is not difficult for one to embrace who is conscious so often of being blind himself, and having so frequently observed it in others. The author would likewise with the utmost diffidence suggest that it is probable that much of the misunderstanding respecting this subject may be due to mistakes in diagnosis, since it seems on the whole not improbable that a great many of the cases observed in institutions for the insane have not been really pellagra, but have belonged to that peculiar and indefinite group of mental maladies that have been together included under the term "pellagra of the insane."

In concluding this phase of the subject it may be said that in the pellagrous insanities the feature most likely to challenge the attention of the average medical man is a profound melancholy, accompanied often by mutism, a disinclination to exertion, and a stereotyped character of movement, which gives the patient an automaton-like appearance; these patients likewise appear to be, as a rule, very sly and suspicious, and if thought unobserved will frequently do things that we would not expect from their general behavior. The author has seen no great number of cases of this kind, and cannot therefore speak with any authority, but it may be mentioned that in private practice, and in cases where there could be no doubt whatever as to the correctness of the diagnosis, friends and relatives have more than once called attention to the patient's only apparant state of insanity,—asserting that they were fully aware of everything going on, and would refer to what was said during conversations days afterwards.

It is much to be hoped that the insanities of true pellagra and those of the so-called pseudo-pellagra will be more carefully studied

in the future, as it is possible that we may be able in this way either or prove or disprove that these two conditions are one and the same.

The mental perturbations that develop in the course of typhoid pellagra should be carefully distinguished from the insanities just discussed, since they frequently occur in patients who have not previously shown marked disturbances of intellect, and the condition is to be looked upon much in the same way as the delirium that is so common in other acute conditions. The patients suffering from this extremely fatal complication present an active delirium, along with the most horrible hallucinations and illusions, ultimately terminating in a profound stupor shortly preceding death.

Atypical forms.—As already indicated, this protean malady appears to manifest itself in chronic disorders of special organs, or in the guise of certain maladies which are ordinarily looked upon as distinct diseases. Among these may be mentioned acidosis, chronic gastroenteritis, essential anaemia, Addison's disease, chronic degeneration with consequent atrophy of various organs, thyroid disease, amyotrophic lateral sclerosis, tetany, paralysis agitans, pseudo-meningitis, psychoses, typhoid pellagra, and *pellagra sine pellagra.* Since each of these different conditions has been thoroughly considered in the chapter on symptomatology, it is not thought necessary to complicate a consideration of the diagnosis by going into details as to the manifestations presented by them,—this being felt to be all the more unnecessary, inasmuch as the names of the different morbid states referred to are in themselves quite sufficient to indicate to the medical mind their individual characteristics.

Pellagrous degeneracy.—Nothing is clearer in connection with this subject than that the pellagrous intoxication makes itsef felt more and more from generation to generation, and that a time is ultimately reached when the descendants of the victims of this malady present distressing malformations and deformities, usually accompanied by pronounced constitutional weakness.

Such offspring of pellagrins exhibit a disproportion between their age and general development both mentally and physically. Anomalies are extremely common, consisting in a variety of pseudo-hydrocephalus, with softening of the bones, flattening of the dental arch, pronounced frontal and occipital protuberances, incomplete ossification of sutures, prominent veins, imperfect development of the skeleton and muscles, large unsymmetrical belly, a long and small thorax, and pitifully short and thin lower extremities.

Such patients are born into the world with an imperfect constitution and a tendency to malassimilation, indicated from the beginning by a lack of normal development, and they quickly show one or more of the symptoms usually associated with such states. There are deficiency in adipose tissue, pallor and yellowness of the skin, a violaceous aspect of the visible mucous membranes, occasional edema of the face and hands, associated with which there are either acute or chronic disturbances of digestion, exhibiting themselves in lack of

appetite, vomiting, and diarrhoea, all of which may be accompanied by cerebral atrophy, idiocy, and nanism. There are also occasionally seen in children the wrinkled skin of senility, fleshy lips, flat nose, hair thin and fine, absence of hair on the body, rudimentary genital organs and lack of development. A large number of these unfortunates die during early childhood.

Pellagra in childhood.—Typical pellagra—even in infants less than a year old—is occasionally seen in childhood, with all of the classic symptoms.

In a certain proportion of cases—and it is probable that the victims are all descendents of pellagrins—dermal alterations occur which may or may not present the typical pecularities of the classical form of the disease; there is also here *pellagra sine pellagra,* so that many of the patients present the general symptomatology of the disease, minus the skin symptoms. Inasmuch as these types correspond in every essential particular with the clinical forms observed in adults, no good could be accomplished by repeating here a description of the clinical phenomena that occur, it being only necessary to refer to the fact that the disease, at least in America, is much less severe in children than in adults.

Laboratory Diagnosis.

With the object of improving our clinical diagnostic methods in pellagra much laboratory work has been done within recent years, but unfortunately it cannot be said that the results are so far commensurate with the great amount of time and attention that have been devoted to the matter; however, for the sake of completeness, a brief *résumé* of the principal results of such investigation will now be given.

Urine.—There is no characteristic change in the urine in pellagra, though it offers in some of its alterations perhaps the most important data on diagnosis obtainable by means of laboratory investigation.

As was long ago determined, the quantity of urine is decreased in this disease, as is likewise usually its specific gravity,—becoming extreme where polyuria exists. The acidity is decidedly decreased. Elimination seems to be somewhat more rapid than in health, while the mollecular state of the fluid is increased, as shown by cryoscopic examination. As has been long known urea is decreased along with the sulphates and phosphates, while on the other hand there is an increased elimination of chlorides.

The facts just referred to have been taken advantage of by Camurri (6) in the construction of a diagnostic formula, which may be stated as follows:

"Any person living under the conditions such as occur where pellagra is endemic, and who for six or eight days on a constant diet shows a decreased in the acidity and increase in the chlorine of the urine, and who shows maize precipitin on blood examination, is already a pellagran" (reference to the writer's method of making the blood test will be considered in its proper place).

It has been thought that both indican and phenols occur in the urine of pellagrins in increased amounts, and that the latter is in greater quantity proportionately than the former—which if true may perhaps be of a certain diagnostic significance, and is likewise of interest in connection with an explanation of the phenomena of intoxication; increase of phenols is, however, seen in other diseases.

As regards the abnormal constituents of the urine it may be said that in rare instances sugar has been observed, and that now and then evidences of a nephritis are encountered, there being a few tube cases and a small amount of albumin; on the whole, however, pellagrous patients seem singularly free from the disorders ordinarily indicated by the changes in the urine, and it has seemed to the author that this is peculiarly the case in America.

As indicating disturbances of the pancrease it is of interest to observe that Gatti (2) has found the Cammidge reaction in the urine in thirteen out of eighteen patients examined.

Blood.—Within recent years the composition of the blood in pellagrins has engaged the very serious consideration of quite a number of investigators, and a large number of careful and accurate examinations have been made,—without, unfortunately, anything being discovered of real importance.

As has been long known, the number of red cells is somewhat decreased in this disease, and where the anaemia is pronounced there may be slight variations in size and irregularity in form of these elements; such variations, however, are always slight and never present the pronounced changes which are encountered in pernicious anaemia or leukaemia; likewise nucleated red cells have never been discovered.

The haemoglobin is almost always less than normal, its diminution being out of all proportion to the decrease in red cells; not infrequently this condition is so pronounced that the blood presents the typical peculiarities of chlorosis.

It is interesting to note that Lucatello (1) found in some instances that the iron content of the blood was considerably greater than was warranted by the quantity of haemoglobin,—being double in some cases.

Much has been written in recent years concerning the increase in white cells, it having been asserted by some who were quite unfamiliar with this malady that this change is a constant feature in pellagra, and that this is a certain indication of the parasitic nature of the disease. On the other hand real observers have demonstrated that the increase in white cells is inconstant, though occurring in a majority of cases, and they have further made it quite clear that the leucocytosis is, practically in all instances, slight, rarely going above 12,000 or 15,000 to the cubic millimetre, and for the most part the number is less. Much more probable is the explanation given by some that these changes are simply those that are the result of the patient's bad assimilation, and may be considered as a blood

reaction to a form of starvation, or represent a reaction of the organism to the changes in the skin and mucous membranes.

As a general rule the small mononunclears are relatively increased, as are also in some instances large lymphocytes and the eosinophiles.

It is noteworthy that careful and patient investigations carried out by a large number of competent observers have failed to show the presence of animal parasites in the blood.

It is likewise true that the blood is free from bacteria, as is abundantly shown by results of many examinations. It is true that Tizzoni has claimed to have found a peculiar polymorphic organism in the blood of pellagrins, but in addition to the fact that others, carefully following his technique, have been unable to duplicate his results, it is true that the description given by him of these germs is such that no unbiased critic could for a moment consider their validity; it is certain that this distinguished observer has been led astray by his ardor, as there can be no sort of doubt that he has described a number of different organisms varying from bacilli to cocci, which in addition to differing morphologically showed dissimilar cultural peculiarities.

Toxic properties.—Observers are not in agreement as to whether the poisonous properties of pellagrous blood are above the normal or not. On the one hand it is asserted that the toxicity of this fluid is little if any increased, and in some instances even diminished, while on the other hand evidence is not lacking that, at least in some cases, this property is above the normal. By injecting eggs with normal and pellagrous serum it has been determined by Ceni (1) that evidences of disturbances in the embryo are considerably more common than where the latter is used. In confirmation several investigators have determined that endo-venous injection of the serum from pellagrous blood produces in the rabbit intoxication and death, though the quantity of serum necessary is considerable, being from 10 to 15 c.c. to the kilogramme of body weight. Gosio and Palladino endeavored to so modify the test as to make it a practical means of diagnosis. They determined that the injection of a very small quantity of this serum into the cranial cavity of a sparrow is followed by stupor, convulsions, and death in a little more than an hour; somewhat greater amounts were necessary when pigeons are used, death only being produced when one-half c.c. of the serum is employed. They likewise found that 1 c.c. of the serum injected into the peritoneal cavity of rats produce tremors, while double this quantity causes death. Employing this test these writers found that positive results were obtained in a great majority of cases in the first, and in all cases in the second stage of the disease; the test was not so satisfactory in the third stage.

Unfortunately these investigators observed positive results in non-pellagrous patients with simple, febrile intestinal intoxication resulting from gastroenteritis, and even in an instance of thermal dermatitis of the backs of the hands. It therefore seems that the

heightened toxicity of pellagrous blood is probably the result of absorption of poisons through the intestinal walls as a consequence of erosion of the epithelial coating, and, in the case of pellagra, the results seem to have some relationship to the eating of maize, since the test often fails if the patient has abstained from this cereal for sometime beforehand.

It is interesting to observe that some writers claim that animals sensitized by repeated injections of maize extracts for a period of fifteen to twenty days exhibit profound disturbances and even die when they are injected with small quantities of pellagrous blood.

Agglutinins.—The first experiments made on the biologic properties of the blood were those of D'Ormea (1), who gave particular attention to the investigation of the agglutinating power of pellagrous serum on the red cells of various animals, but he was unable to find any marked variation from the normal; nor could he observe any unusual action of the sera of animals on the red cells of the pellagrin. Later, similar experiments were made by Carletti (4), who was of the opinion that the serum of pellagrins comports itself in its action on the red cells of normal individuals in much the same way that it acts on those of the diseased, but he thinks that there is in the latter slight evidence of increased agglutinating power.

As regards various bacteria, the results have been equally fruitless, it having been shown by Gosio and Palladino that the Widal test is not given by pellagrous blood with the various bacteria grown in culture coming from the intestines of dogs poisoned with maize. This subject has been also particularly investigated by Babes and Busila, who have made almost every conceivable test of this kind without positive results.

Precipitins.—Following the well-known observations of Krauss on the production of precipitins in the blood serum, this subject was shortly thereafter examined by D'Ormea (1), who found that the serum of pellagrins produces a precipitate with extracts of the cellular protoplasm of the tissues of animals, and also with those of the organs of other persons suffering from this disease.

These experiments were later repeated by G. and S. Gatti, who are inclined to think that the precipitate produced by adding the serum of a pellagrin to an emulsion prepared from the organs of another pellagrin is specific. The technique of the examination is carried out as follows:

The ground organs of pellagrins are mixed with a physiologic salt solution in the proportion of one to ten, and 2 per cent. carbolic acid added for preservation; after twenty-four hours at a temperature below freezing some of the emulsion is decanted, and placed in a thermostat with some of the serum from the blood of another pellagrin. After half an hour there develops a dense precipitate which is particularly marked where extracts of the pancreas and the adrenals are used.

Somewhat later Gosio and Palladino, following the suggestion of Lanzetta, made a number of investigations and determined that the serum of pellagrins gives a precipitate when mixed with an extract of bad maize. The test is carried out as follows:

They prepared a mixture of 100 grammes of maize meal and 100 c.c. of physiologic salt solution, which is set aside for eight hours, with occasional shaking. The extract is then filtered and refiltered through the same filter paper until the liquid comes away clear; if it is not to be used at once 0.3 per cent. of phenol is added. If the solution is to be kept for a long time—the writers never used it after forty days—they pass it through a Berkfeld filter and divide it into 5 c.c. portions, which they put up in small sterile glasses and seal with heat.

To the infusion thus prepared the serum is added in amounts which should not be less than 0.5 c.c. to 5 c.c. of the extract, since it is observed that if a smaller quantity be used the precipitation is so slight that it may be overlooked; to get the best results 1 c.c. or more is advised. After being mixed the test solution is placed for four hours in an incubator at 98.6° F. (37° C.) in order that the precipitate may have time to deposit. Only such tests are regarded as positive as give with at least 0.5 c.c. of blood a marked precipitate; where the test solution simply gives a turbidity the result was regarded as negative.

Pursing these experiments still further Gosio and Palladino determined that precipitins do not occur in the blood of normal persons who regularly eat maize. Remembering that various observers had been able to discover evidences of immunity in animals by feeding them certain poisons by the mouth, and taking into consideration the fact that it has been shown that antibodies are not produced if albuminous foods are well chewed, and recalling that immunity is not produced in adult dogs, but does occur in young animals, experimented upon before pepsin and hydrochloric acid begins to form in their stomachs, it occurred to these acute investigators that it was not improbable that their results were after all only the consequence of the bad state of the digestion of pellagrins, and that often the ulcerated surfaces of their intestines allow the maize albumins to pass directly into the body without being denatured; on investigation it was abundantly proved that this suspicion was correct in both men and animals.

Similar conclusions have been arrived at by Camurri (5), who agrees with the investigators already referred to that the occurrence of this precipitin in the blood simply shows that the person from whom it comes is an eater of maize, and that he has recently had a lesion of some kind of the gastrointestinal tract. It is of interest to note that Camurri observed that in animals this power of producing precipitins gradually decreased in from three to six weeks, ultimately to disappear entirely, quite irrespective of whether the animal continues to receive the injections of maize or not. This is in entire accord with the experiments of Nuttall and Tchistowitch, who have conclusively shown that the precipitins are evanescent, and are

to be regarded simply as accessory phenomena in the production of immunity.

In this connection it may be mentioned that Centanni (1) maintains that the presence of autocytoprecipitins indicate a reaction of the organism against certain substances produced by the diseased organs, and Carletti (4) very properly observes that the intestinal lesions might well be the result of the action of other toxic substances or of bacteria, and that under such circumstances proof of the entrance of the maize albumins into the body fluids would be of no value.

Maj (2) has experimented on this property of pellagrous blood by the methods of Porges-Meier and of Elias-Neubauer.

In the former the serum of the patient is diluted with salt solution 1 to 5, and 1 c.c. of this mixture is added to 0.2 c.c. of a suspension of Merck's lecithin, after which the solution is set aside in a test tube at the temperature of the body, and examined every hour for evidence of the formation of precipitates.

The latter method consists in the addition of a 1 per cent. solution of Merck's glycocolate of soda to pellagrous blood serum, and the whole set aside at ordinary temperatures for twenty-four hours. As might have been expected, no results of any importance were obtained from these tests, the pellagrous blood comporting itself in every way like that of normal individuals.

Lysins.—No very great amount of attention has been given to an investigation of the lysins of pellagrous blood, though the subject was early attacked by D'Ormea (1), who found that there was no obvious variation from the normal.

Somewhat later investigations by G. and S. Gatti have shown that the serum of the blood is not autolytic, though it shows at all stages of the disease an increased haemolytic power for the blood globules of the same species, and for those of different species.

Tizzoni (5) has recently asserted that pellagrous blood contains anti-haemolysins, his test being carried out in the following manner: A couple of drops of fresh defibrinated rabbit's blood is added to a test tube containing 10 c.c. of common broth, rendered isotonic with a proper amount of salt; if now to this mixture 0.2—0.3 c.c. of the serum of normal human blood be added, and the mixture left in the thermostat for twenty-four hours, it will be seen that the blood cells sediment slowly, and that haemolysis manifestly occurs to a marked degree. If, however, instead of using the serum of normal persons that of a pellagrin be employed, and if the mixture be afterwards treated in a similar fashion, the blood cells will settle to the bottom without any solution of the haemoglobin occurring. Zuccari has repeated these experiments, but unfortunately was able also to find that the serum of non-pellagrous persons frequently acted in much the same way as that of pellagrins.

Complement fixation.—The idea that the Wassermann reaction might be obtained in pellagra appears to have originated with Bass,

who reported a number of years ago results which were most encouraging. The test was carried out in the usual fashion,—lecithin being used as antigen. Very quickly thereafter Fox reported the results of this test in thirty cases of pellagra, and found it only strongly marked in one instance. Similar results have been obtained by Carletti (4), Babes and Busila, Raubitschek (3) and Lucatello and Carletti, all of whom agreed that nothing was to be expected from this test in pellagra. The last named observers investigated this subject very thoroughly, using all of the internal organs of pellagrins as sources of antigen; it is interesting to observe that three or four non-pellagrous syphilitics gave positive results with antigens obtained in this way,—which is but another illustration of the uncertainty of this procedure, whatever may be the disease with which we are dealing.

It is likewise of interest to note that Carletti (4) and Alvisi have been unable to get positive results by the meiostagminic method of testing complement fixation devised by Ascola,—this curious development of latter-day medicine being based on the alleged capacity of specific antigens to cause a diminution in the superficial tension of human sera.

It is perfectly clear then from the foregoing that we need not look in the future for aid in diagnosis from tests having as their basis complement fixation. The results here appear peculiarly uncertain, which is saying much.

It is of interest to note that Besta (6) has investigated the biologic properties of pellagrous blood, and also that of animals poisoned with extract of bad maize, and has entirely failed to find anything abnormal.

In concluding this subject it is only necessary to call attention to the general uncertainty and extremely unsatisfactory results that have been obtained, and to remark that there seems little doubt that no reliance whatever can be placed on biochemic reactions from a diagnostic standpoint in pellagra. While it must be admitted that competent observers have in many instances described reactions that are generally supposed to be connected with the production of immunity, it seems certain that at best their only significance in this connection is that they indicate the probability that the person from whom the blood is taken has been in the habit of eating maize products for a period immediately preceding the time that the examination is made —a fact which could be much more easily ascertained in other ways, and which could have little or nothing to do with any pellagrous symptoms from which he might be suffering. In any case results of this character could only relate to a toxic condition resulting from the action of albumins, as it is generally recognized that the system does not give the peculiar reactions under discussion to poisons of a different character. According to the views of those who have most right to an opinion, it seems extremely probable that pellagra is the result of the action of certain poisons produced in maize by moulds, and that these toxic substances belong to the group of phenols; if this conception be correct we should not then be disappointed if we are

unable to obtain characteristic biochemic reactions, nor should we hope to secure anything like immunity in the sense in which the word is generally employed.

It may not be out of place to point out that the results of blood alaysis are quite in keeping with the author's conception of pellagra; if this be correct we could hardly hope for any other issue in an intoxication, resulting from poisons belonging to the phenol group, that has perhaps gone on in the majority of instances for from twenty to forty years, and which probably in most if not all cases began during foetal life, and in which the symptoms are not manifested as a consequence of the direct action of the toxine, but are produced by a gradual destruction of nerve cells, and a general deterioration of the entire body. When it is further remembered that the lesions referred to may have been produced many years before, and that the pellagrin may not have consumed any maize at all in the meantime, the likelihood of his blood giving rise to biochemic reactions similar to those that are sometimes obtained in acute morbid states the result of toxalbumins seems still less probable.

Quite recently Nitzescu has attempted the diagnosis of pellagra by employing the Abderhalden test for protective ferments, and has obtained results that seem to indicate that such substances exist for zein. He investigated fifty-eight cases of pellagra and found the reaction clearly positive in fifty-one, weakly positive in five, and negative in two old cases. Control experiments with glyadin and bean meal gave negative results. With what one might describe as biochemic enthusiasm the author naturally concluded as the result of his experiments that zein is the one and only cause of pellagra.

However, inasmuch as the technical difficulties in carrying out this test are considerable, the author hardly feels that further space should be taken up with a discussion of the methods employed. It is perhaps enough to say that zein, of course, takes the place of the tissues which are ordinarily employed in carrying out this test, and that otherwise the usual technique is employed. Those who are particularly interested are referred to the paper of Nitzescu.

Hypersensibility to maize extracts.—The idea that it might be possible to produce anaphylactic phenomena in pellagrins by the injection of maize extracts appears to have originated with Devoto (2). In 1901 this eminent investigator had his assistant Ascoli to inject watery extracts of fermented maize into fourteen pellagrins, which was followed in every instance in four or five hours by a marked febrile reaction, that was maintained in some of the patients for seven or eight hours, and which in some cases recurred on the following day.

Many years later similar investigations were made by Volpino, Mariani, Bordoni and Alpago-Novello (1, 2), who have written a number of papers detailing the results of their experiments. Their findings may be said to confirm fully those of Devoto; practically in all instances the subcutaneous injection of an extract of bad maize was followed in a few hours by malaise, dyspnoea, nausea and elevation of temperature of from 1° to 3°; there were also recrudescence

of the erythema—in one case an eruption occurred where none had existed previously—diarrhoea, stupor, somnolence, marked nervous and psychic excitement, tremor, loss of memory, and in one case coma; at the point of puncture the tissues were red and painful. These symptoms persist as a rule for from two to three days. In one of their series of experiments twenty-three non-pellagrous persons were injected with this extract, and though some of them developed slight fever, there were no general symptoms. Extracts of sound maize produced no more results in pellagrins than in normal individuals.

The solution employed was prepared in the following manner: They extracted meal from bad maize with physiologic salt solution for some hours at a temperature of from 55° to 60° C.,—the mixture in the meantime being frequently agitated: the extract was then filtered through paper and afterwards through a porcelain filter. The filtrate was then placed in flasks for from twenty-four to forty-eight hours at 98.6° F. (37° C.); the clear supernatant fluid was then drawn off from a precipitate which forms during this process. From 1 to 2 c.c. of this liquid is injected. The authors in no place inform us as to the exact proportion of physiologic salt solution and meal employed.

In later experiments these investigators endeavored to determine if it were possible to separate from the extract the principle that produces the peculiar reaction referred to; after some investigation it was determined that this was possible by the following manipulations:

The extract is reduced on the water bath to one-tenth of its original volume, after which twenty parts of absolute alcohol are added, which is followed by an abundant, whitish, flocculent precipitate; this precipitate is then washed three or four times in alcohol and thoroughly dried; the resultant powder is then dissolved in physiologic salt solution in an amount corresponding to the original extract.

This solution was found to be entirely harmless to animals and normal persons, but produced a violent reaction in pellagrins. It is noteworthy, however, that they assert that the results following the injection were not quite so certain as when the simple extract was used.

The precipiate is very resistant to heat, not being destroyed at 239° F. (115° C.). It is called by these investigators *pellagrogenina*. It is a curious fact that this substance is also yielded by extracts of good maize, although no such effects as follows its injection into animals can be obtained from the injection of the liquor from which it is prepared; it is therefore obvious that there is some neutralizing agency in sound maize, which is destroyed when it becomes mouldy, since extracts of the latter act just as does pellagrogenina.

Operating on more than 265 pellagrins and 78 healthy people these writers found that when they are inoculated with a 1 per cent. solution of pellagrogenina in normal salt solution in the muscles of the gluteal region 90 per cent. of the former and 20 per cent. of the latter give the reaction. A 10 per cent. solution gives a skin re-

action when used in the same way as is tuberculin for the production of the well-known reaction for tuberculosis.

These investigators were unable to obtain specific reactions either as regards precipitins or fixation of complement by using pellagrogenina and the serum from pellagrins.

This subject has also been investigated by Cesa-Bianchi, who found that a marked degree of hypersensibility to maize extracts was developed in animals after they had been fed for a time on either good or bad maize.

Not so satisfactory were the experiments of Ezio, who obtained positive results in only two out of five cases of pellagra, and who found that in three normal individuals a reaction followed the injection which was quite as marked as that obtained in the two pellagrins.

This subject has likewise been thoroughly investigated by Rondoni (1), who was only able to obtain positive results in 60.72 per cent. of his pellagrous cases, nor did he observe after the injection the marked symptoms described by Volpino and his associates; however there occurred in positive cases some elevation of temperature, along with malaise, headache, neusea, rheumatoid pains, nervousness, and insomnia, all of which passed away in a day or so.

His directions for preparing the extract are somewhat more specific than those of the authors already cited. The maize is ground up in a common iron mill, and mixed with physiologic salt solution in the proportion of one part of the former to four of the latter by weight, and the mixture placed in a water bath for some hours at a temperature of from 112°—140° F. (50°—60° C.), after which it is filtered through paper, placed in bottles, and sterilized; on heating there is a slight precipitate which is diffused through the extract by shaking just before the injection.

In some of the experiments he used one part of meal to two parts of the salt solution. He observes that inasmuch as the active principle is not destroyed by boiling, it suffers no deterioration during the process of sterilization.

The injections were made in the thigh or buttocks after the parts were thoroughly sterilized.

It is interesting to observe that this investigator made some observations on the effect of the injection of extracts of wheat and of chestnuts, there having been twenty-three experiments carried out with the former and five with the latter; no reaction whatever was observed in the former, while in two of the latter there was slight malaise after the injection.

Of interest and significance are the results of Ghirardini and Zuccari, who, after feeding twenty-two guinea pigs for from sixteen to thirty-six days on maize—both good and mouldy—found that they showed marked anaphylactic phenomena when injected with 2 to 3 c.c. (30-45 minims) of the serum of pellagrins; the injections under the skin failed to produce marked results, but when the serum was introduced into the peritoneal cavity there was depression of temperature (0.5—3.5° C.), convulsions, dyspnoea, paralyses, incoördination,

and the hair becoming erect; these symptoms were much more pronounced where the animals had fed on bad maize. Volpino, Mariani, Bordoni and Alpago-Novello (2) also found that if guinea pigs are fed on bad maize for from fifteen to twenty days they die in twenty-four hours after being given subcutaneously 0.5—1 c.c. (7.5—15 minims) of serum from a pellagrin. If true, this procedure might prove to be of much diagnostic value.

Rondoni is not entirely certain of the proper interpretation of the results of his experiments, only asserting that we may regard the reactions obtained as being anaphylactic in character.

In concluding this subject it should be observed that hypersensibility of pellagrins to maize extracts is probably in no way specific, since, like the blood reactions already referred to, it seems simply evidence of the fact that the patient has at some time been a maize eater, and that during this period there probably occurred lesions of the intestinal tract of such character as to permit the absorption of unaltered maize albumins.

On the other hand we should not forget that a state of hypersensibility could doubtless result from the absorption of the phenol poisons of bad maize, and of course might occur where there had been no abrasions of the mucosa of the alimentary tract; should this prove to be the case the reaction might prove to be of more value than the tests that depend on precipitins, complement fixation, etc.

Differential diagnosis in the first stage.

Nervous dyspepsia.—While the diagnosis of a well-marked and typical case of pellagra offers no difficulty to those well versed in the clinical characteristics of the malady, the matter is by no means so simple where the case is seen in its earliest stages; at this period, as a matter of fact, the symptoms are usually regarded as being of but little importance, and the patient is dismissed with the assurance that he is "bilious," or is in a run-down condition from some one of the causes that usually produce such a result.

Where the malady has progressed somewhat further the symptoms are in the main those of "dyspepsia," for which the medical attendant usually prescribes remedies employed in cases of this kind, and again the victim is assured that his condition is in no way serious.

After the malady has persisted for some years the patient is very apt to fall in the hands of stomach specialists, where he is again treated, with more or less benefit, for whatever obvious functional disturbance in the digestive processes from which he may suffer. Even at this period the patient has become more or less cachectic and is commonly quite thin, and relaxation in the abdominal walls, with more or less ptosis of the viscera, is extremely common—particularly in women. Examination shows that the stomach sags, and in female pellagrins there is quite commonly a movable right kidney easily perceptible below the costal margin, and coloptosis is found on x-ray examination.

An analysis of the stomach content usually results in its being determined that the hydrochloric acid and gastric ferments are absent or much reduced in amount, a condition which accurately corresponds with the results of physical examination. Thus far the clinical picture is that of a condition, with the accompanying digestive disturbances, that is very common in men who have led sedentary lives, who have overworked, and who have not given that attention to their health which common prudence would demand; even more likely is this state of affairs to be found in women school-teachers, and in those who have borne children rapidly and often, or who have been compelled to manage their households with inadequate assistance.

Where the case is pellagrous, however, there always occur in addition certain symptoms that will usually point the way to a correct diagnosis.

In addition to the constipation, which is also frequent in ordinary disturbances of the digestion, it may be determined on inquiry that the patient has for a number of years felt much worse in the spring, and in all probability it is at this season that he first seeks advice. It will be found that he has suffered from dizziness in almost all instances, that he has at times had soreness of the tongue, or of the lips, that a peculiar burning sensation in the mouth, throat, esophagus, stomach, backs of the hands, or feet is complained of, that there is a very curious and most marked mental and physical depression, with great weakness of the legs, together with anorexia, globus hystericus in women, and the gastric disturbances already mentioned.

It is especially worthy of attention that while the symptoms of altered digestion differ but little throughout the greater part of the year from those encountered in what is called "nervous dyspepsia," the manifestations observed in pellagrins become more pronounced in the spring, and do not show the variation from day to day that is so commonly seen in ordinary indigestion.

Patients suffering from the mild or very chronic forms of pellagra frequently develop the curious furrows on the surface of the tongue, which, when present, are of much diagnostic importance.

In the more chronic forms of the disease the tongue is tremulous, is frequently smaller than normal, cannot be properly protruded, or its edges turn up or down unnaturally, and, of still greater importance, the lips, gums, buccal mucous membrane and throat may show the peculiar lividity of the mucous surface that is diagnostic when present.

Lastly it may be said that these patients, as pointed out by several observers, present a rather peculiar facies in which melancholy and anxiety are written, along with slow and uncertain movements, and a general air, which, after being once recognized, is difficult to mistake.

Hypochondria.—The peculiar manifestations that are so characteristic of hypochondria are likewise frequently encountered in the earlier stages of pellagra, and particularly make their appearance during the later winter months or spring. So closely do the two diseases approximate each other that it has even been suggested by some that

they are identical,—this view having been particularly urged by Videmar. Indeed it may be said that these affections so much resemble each other that a differential diagnosis is often very difficult, at least for a number of years, and it is only after observing the seasonal development of the pellagrous symptoms, and the gradual but steady decline in the patient's health that a diagnosis at last becomes possible. In some instances the furrows on the tongue, the livid mucous membranes, the continuous vertigo, the burning in the mouth, esophagus, and stomach, or in the backs of the hands, along with all of the symptoms becoming much more pronounced in the spring, make the diagnosis easy, even in the earliest stages of the malady.

Both classes of patients suffer extremely at times from what is called "nervousness."

Lastly it may be mentioned that hypochondriasis is preëminently a disease of the well-to-do, while on the other hand pellagra is very largely a malady of the poor.

Hysteria.—In the earliest stages of pellagra, and during the period of depression that precedes a classical outbreak of the malady, marked hysterical manifestations are extremely common in women. Under such circumstances the diagnosis will have to depend largely on the history of the case, for while in typical hysteria the patient may remain in much the same condition year after year, this is never the case in pellagra, the tendency always being gradually to get worse and worse. As a differential point in the diagnosis we may also here again invoke the seasonal exacerbations which are so common in the latter disease. Likewise of importance are the occurrence of pronounced vertigo, burnings in the backs of the hands or in the stomach, the furrows on the tongue, and the livid mucous membranes.

It is also noteworthy that the hysterical patient is not uncommonly in good physical condition, while the contrary is almost invariably true of female pellagrins, though exceptions do occasionally occur; it is also true that hysteria affects all classes, with rather a preference for the well-to-do, while pellagra is preëminently a disease of the toiling multitude, and particularly of those who constantly expose themselves to the vicissitudes of the weather.

DIAGNOSIS IN SECOND STAGE.

Parapellagras.—As has been before remarked, the manifestations that occur in a typical attack of pellagra are of such character that it is difficult to mistake them. However, it has been quite clearly demonstrated that patients occasionally present symptoms that closely simulate those of the pellagrous state, notwithstanding the fact that the stricken individual has never at any time eaten maize products. As before pointed out, it has been held by the advocates of the maize theory that such instances are really not typical examples of pellagra, —this view being based not only on the absence of the generally accepted etiologic agency, but also quite generally upon certain differences in symptomatology, to which attention will be presently directed. It cannot, however, be reasonably doubted that it is possible for

pellagra-like symptoms to be produced by agencies not ordinarily operative in this disease, and it is therefore highly probable that we may have pellagroid affections the result of poisons that differ from those that produce the classical type of this malady; for such conditions the author has proposed the general name of "parapellagra."

While it is unfortunately not possible at the present time accurately to separate the different parapellagras from each other, it would appear that there are at least three distinct clinical forms, and that they evidently constitute symptoms-complex produced by totally different causative agencies.

Alcoholic parapellagra.—Probably the most common, and clearly the best understood, of these varieties of parapellagra is that which is produced by alcohol.

As has been already remarked, clinicians are in very general accord as to the occurrence of a peculiar inflammatory condition of the skin brought about by the long-continued use of alcohol. Inasmuch as this skin lesion not uncommonly makes its appearance on the backs of the hands—a situation where the resistance is naturally low—it has not been uncommonly mistaken for the erythema of pellagra,—particularly as at certain stages it presents a decided resemblance to the lesions that occur in this affection.

It is furthermore true that such patients not uncommonly suffer from loss of appetite and marked digestive disturbances, including diarrhoea, and when there is added to this the nervous symptoms and mental disturbances frequently observed as the result of over-indulgence, the resemblance to pellagra becomes so marked that it is not strange mistakes have now and then occurred.

While it is true that the external manifestations produced by alcohol may occur at any period of the year, it is most interesting to observe that here, as in other intoxications, the most marked and pronounced disturbances are peculiarly prone to occur in the spring and early summer. On the authority of Roussel (3, p. 131) it is said that Bang, of Copenhagen, observed that between 1826 and 1829 the majority of 456 cases of delirium tremens occurred during the months of May and June, and Hoegh-Guldberg, also of Copenhagen, has noted that from the years 1830 to 1832 double the number of cases of this kind occurred in May than in all the other months together.

Notwithstanding the fact that we may have in alcoholism the simultaneous development of skin, intestinal and brain symptoms, with a pronounced tendency to come on in the spring, there should certainly be in the great majority of cases no difficulty in differentiating this symptom-complex from pellagra.

To begin with—and this is of much importance—we should always keep in mind the causation of symptoms that result from alcoholism, and should never make a diagnosis of pellagra in a patient who is known to be addicted to over-indulgence in this narcotic without going most carefully into the clinical history, and assuring ourselves that the pellagrous element really exists.

Under such circumstances the general condition of the patient should be first taken into consideration. In alcoholism the body is as a rule well preserved, and the subcutaneous fat rather increased than diminished, a condition that is quite the opposite to that usually encountered in pellagra. In the former there is likewise tremulousness, beginning in the hands and passing quickly to the arms and lips; this symptom is particularly marked where the patient shuts his eyes and with the lips closed draws the corners of the mouth outward as far as possible. The speech becomes embarrassed and hesitating, and weakness comes on, first manifesting itself in the upper extremities instead of the lower, as is the case in pellagra. It is further true that coördination of movement is much disturbed in alcoholism, while on the other hand in pellagra such results are uncommon, and as a consequence this symptom becomes of much importance in cases of doubt; as an effect of this prehension is much interfered with, and the gait is staggering. Of much importance also is the fact that weakness in the lower extremities is an early and most common symptom in pellagra, a point in the differential diagnosis to which Dejeanne has particularly called attention. As a result of the general neuritis we also find in alcoholics a profound alteration of sensibility manifested by tingling in the hands and feet, with hyperaesthesia and anaesthesia. Convulsive phenomena, weakness, vertigo, and disturbances of the special senses, may occur in both maladies, but the first of these is decidedly more common in alcoholics.

The frequency of skin alterations of the face are so common in chronic alcoholism that they are generally regarded by the laity as being the most distinctive symptome produced by over-indulgence. The change is not one that resembles the characteristic erythema of pellagra, consisting as it does generally of acne of a roseceous or telangiatoid form, occurring on the chin, over the nose, around the eyes, and on the forehead. At times the redness approaches in appearance quite closely to the similar condition of the skin of the face seen in pellagra, but a careful inspection would perhaps in all instances resolve any doubt as to its true character; it is further true that this form of skin trouble comes on with extreme slowness, and not like that of pellagra in a few hours, and that it furthermore persists for a long time and does not show the fine exfoliation of the epiderm that begins in the center of the true pellagrous lesion very soon after it first makes its appearance, and which then extends gradually outward to the borders of the dermal alteration. There is never in these alcoholic facial skin lesions the typical change which is known as the "pellagrous mask," a point upon which Merk (3) particularly insists. It is furthermore true that the so-called "Casal's necktie" appears never to be present in alcoholism.

The skin alterations of the backs of the hands are those that are most apt to be mistaken for the pellagrous lesion; however there is never produced, it is said, a distinct pellagrous glove, and not infrequently the lesion is not symmetrical, or limited to one hand alone. According to that distinguished Italian dermatologist Majocchi (4) the lesions on the forearm and arm are apt to be more extensive than

is common in pellagra, and he further observes that the sharp line of demarcation between the diseased and healthy skin, which is so characteristic of pellagra, is not seen in alcoholism. The alcoholic lesions also are exceedingly persistent, continuing almost without change for months or even years, and are only followed by pigmentation at a late period. It is also generally admitted that the peculiar livid color quickly assumed by the pellagrous lesions does not occur in alcoholism. Finally it should be mentioned that desquamation in alcoholic lesions presents itself in the form of large masses of dark gray color, and that actual cracking of the skin does not take place.

It does not appear that the alcoholic lesions have ever been observed on the feet or legs.

It should not be forgotten that sunburn is not at all an uncommon occurrence in alcoholics, and that in this way lesions may be produced that even more closely resemble those of pellagra than those brought about by over-indulgence in the cup that cheers.

The disturbances of the gastrointestinal tract that occur in alcoholism differ markedly from those found in pellagra. In the former there is a coated tongue, bad taste, foul breath, frequently a loss of appetite, and the early morning vomiting with which all clinicians are so well acquainted, while in the latter we have often a salty taste and bad breath, an irregularly coated tongue, often livid mucous patches in the mouth, burning sensations in the mouth, throat, esophagus and stomach, pyrosis, eructations of gas, a feeling of fullness, etc. Particularly in the latter stages diarrhoea not uncommonly occurs in both.

In his interesting article on pellagra in Yucatan Gaumer expresses the opinion that all parapelagras are alcoholic. They differ from true pellagra in that there are no sensory symptoms in the mouth, throat or stomach, and no impairment of taste or loss of appetite. Ocular symptoms generally occur in the alcoholic form, as do also disturbances of locomotion. These patients are cheerful and talkative, but at the same time often express fear of death. The skin changes are confined to the hands, become pregressively pigmented, and large, thick scales form, and, frequently becoming detached, fall off; itching is common.

In both conditions disorders of mentality are common, but those of alcoholism are characterized by sombreness, preöccupation, and a defiant attitude, while the alienation in pellagra takes the form of sadness and great physical and mental depression.

In *delirium tremens* hallucinations play an important rôle, but such mental states rarely occur in pellagra except in the terminal stages, where a condition of so-called typhoid pellagra has supervened.

Parapellagra of misery.—It has long been believed that cachectic conditions may be followed by the appearance of pronounced digestive disturbances, and the occurrence of skin lesions, and the literature is quite replete with cases where it is clear, even from the

history given by the reporter, that the conditions described were not pellagrous, and that they were possibly the consequence of a state of prolonged physiologic misery. Within this category would probably belong two or three of the cases recorded by Strambio, where the patients appeared never to have eaten maize, and where the symptoms are not of a convincing character.

During the succeeding century quite a number of cases of this kind were recorded, but practically without exception the reports emanated from medical men with little, or, most often, no practical acquaintance with endemic pellagra, and while they have almost invariably loudly protested that their cases were genuine examples of this disease, there cannot be the slightest doubt that they were generally dealing either with some skin affection, or with the symptom-complex now under consideration. For the reason therefore that this error is not altogether unusual, this aspect of the subject is of considerable interest from a diagnostic standpoint, and deserves our careful consideration. As to whether there are cases of parapellagra associated with misery which really resemble the genuine disease it is difficult to say, for in no single instance has the author seen a description of such accurate character as would make clear beyond doubt its true nature. That cases of this kind do occur that greatly resemble pellagra appears possible, but unfortunately for lack of clinical data we are hardly in a position to differentiate clearly between them and the endemic disease. However, it should be remembered that the victims of starvation simply complain of hunger and suffer little or not at all, as Dejianne points out, from the peculiar train of nervous and dyspeptic symptoms that are so characteristic of pellagra.

Where, however, instances of the kind are suspected, it would be well to remember the chain of characteristic symptoms that accompany the endemic form of the malady, and a most careful examination of the patient and a thorough study of the skin lesions should be sufficient to make the diagnosis clear.

Parapellagra of the insane.—Perhaps closely associated etiologically with the parapellagra of misery are those much more common pellagroid manifestations occurring in the insane, and upon which so much has been written. Here again we are confronted with the impossibility of deciding as to the true nature of these conditions, since the author is aware of no instance in which a thoroughly adequate description has been given. We only know that erythemas are commonly observed in asylums, and that they frequently come on the backs of the hands, that the victim not uncommonly presents digestive disturbances, sometimes associated with sore mouth and diarrhoea, and that when the skin lesions and the gastrointestinal disturbances are added to the mental state the likeness to pellagra in many instances is striking. Unfortunately a clear comprehension of this subject is greatly hampered by the fact that it is known that in all parts of the world the mentally weak are peculiarly liable to chronic forms of catarrhal enteritis, as was strikingly shown by Bremer, and it is further well recognized that many kinds of insanity are frequently

associated with more or less dermatitis of the hands. In this connection the words of the consulting committee on public hygiene of Paris, uttered in 1859, may be here profitably repeated, since they are to-day quite as true as when given to the world. They say:

"Never has there been a greater confusion in the recognition of essentially different morbid states. Particularly is this true as regards the cachectic diarrhoeas and erythemas of the extremities, which are common in the later periods of depressive forms of insanity, of dementia, or general paralysis, and lipemanic stupidity, and have no sort of connection with true pellagra."

It is so evident that the insane are often attacked by such symptome that it seems to the author that a diagnosis of pellagra should never be made in a case of insanity except with a full knowledge of the patient's history and a most careful attention to detail in making the examination,—especially as regards the skin. From the number of reports that have in recent years flooded the American literature it would appear that there is hardly an institution for the mentally weak in the United States where cases of pellagra have not been diagnosticated; in those regions where maize is a common food it is doubtless the case that many instances of this kind are the result of true pellagra, but in other parts of the country it may well be that mistakes are exceedingly common. If there were no other error in connection with this than a simple misapprehension as to the geographical distribution of pellagra the matter might be allowed to rest without protest, but unfortunately these mistakes in diagnosis are necessarily productive of the greatest confusion in the symptomatology of pellagrous insanity and kindred mental states. It is only in sanatoria for the insane that mental diseases are carefully studied, for it is only in such situations that the patients are under continuous observation, and it is only here that we have experts properly trained for making satisfactory examinations; how great then must be the confusion and how unreliable must be our data respecting the pellagrous psychoses when every patient who has a skin eruption or develops a diarrhoea in such institutions is promptly catalogued as having pellagra! It is not difficut to see the reflex of such unscientific procedures in the totally contradictory views which competent alienists even now maintain respecting the character of the pellagrous insanities—differences that can only be due to inaccuracies in observation, or to misapprehension as to the true character of the disease with which they are dealing. It would therefore be urged by the author that until this whole matter is placed on a scientific and thoroughly satisfactory basis, and until we learn to differentiate clearly the pellagrous psychoses from all other forms of mental alienation—if such a thing be possible—that we only regard those cases as being pellagrous which show a connection with maize eating, accompanied by the symptoms that characterize pellagrous conditions.

In all of these forms of parapellagra attention should be especially directed to the character of the eruption, as it is well-known that there are a number of skin affections that bear a decided resembance to pellagra; it is a matter of record that parasitic skin affec-

tions have been mistaken for this disease, even by Billod, the great protagonist of the movement that sought to show that the asylums of France were filled with pellagrins who had never consumed maize products. It is doubtless likewise true that many of these cases are really instances of sunburn, which presents a rather striking resemblance to pellagra in its earlier stages. If such mistakes can occur, how much more common must be errors in diagnosis between pellagraderms and vitiligo, some forms of eczema, and Hebra's erythema exudativum multiforme, which last mentioned disease so strongly resembles the skin lesions of pellagra both in appearance and location that it is difficult even for experts to differentiate.

In this connection the remarks of Zilocchi (2), who is a really competent pellagrologist, are of interest. He says:

"The erythema of pseudo-pellagra is darker than that of the genuine disease, with absence of the underlying redness; the former phenomena disappear more quickly, as do the erythemas from the sun, and present during the process a lesion that is dryer than that seen in pellagra, and there follows a greater cutaneous dystophy. On the other hand the pellagrous erythema is of a deep red color, which persists for a long time, and the lesion is more profound and is usually much more moist. It is likewise interesting to note that in the true pellagra the color of the skin of the body assumes a yellowish aspect not observed in the pseudo-pellagras, and it is typical of the former that there are many large commodoes on the nose, which assume a yellow color."

Presumably in these remarks Zilocchi refers to all of the forms of parapellagra.

From a study of the cases recorded by Billod (2) in his very extensive work on what he calls the "pellagra of the insane," it would appear that ulcerative processes in the mouth are really quite rare in such cases, but it is apparently true that they occasionally occur. As it is well-known that various forms of stomatitis are apt to make their appearance during the course of digestive disturbances, there is no reason, *a priori*, why such lesions should not be occasionally encountered under these circumstances; here, however, we lack again that careful and scientific attention to detail that is so necessary in matters of this kind,—the reporters of such cases uniformly satisfying themselves with the simple statement that the patient presented some sort of lesion in the mouth. It is interesting to observe that Landouzy asserts that the deep furrows so often seen on the tongue in pellagra are common in the so-called pseudo-pellagra, but a careful perusal of the clinical histories of the twenty-five cases which he has reported, as well as of seventeen others collected by him from the literature, shows but a single instance where mention is made of this condition.

In concluding this phase of the subject reference should be made to the fact that there are a number of cases in the literature where patients—reversing the general rule—have first shown skin and intestinal disturbances, and only developed mental changes at a later period. In just what category such forms of parapellagra belong it

is difficult to determine, but it would appear that they are after all not radically different from those cases where the order of the pellagroid manifestations is reversed; certainly there appears no reason why the causes that give rise to the skin disturbances may not operate quite as well before as after the development of pronounced mental alienation.

Cases reported as pellagra that clearly belong in some other category are not at all uncommon in medical literature, and are especially frequent during those periods when some particularly enthusiastic individual takes it upon himself to prove with a few imperfect clinical histories, that pellagra has no connection with maize, and is encountered the world over. During revivals of this kind a certain number of converts may be counted upon to assist the cause by demanding that the profession, and particularly that part of it experienced in the subject, accept as genuine pellagra a choice and assorted collection of more or less bizarre and unusual form of common skin and nervous affections.

Thus we find that Billod (1) presented to the Academy of Medicine of Paris three cases of alleged pellagra which he had selected from the asylum for the insane at Sainte-Gemmes as typical of this disease, and defied men and pellagrologists to prove the contrary. On close inspection, however, two of his hearers, Doctors Cramoisy and Pouquet, observing that in these cases the hair was coming out at the point where the disease was most marked, were able to determine on further examination that they were covered with masses made up of the tricophyton. Somewhat later Bazin had occasion to look into this matter further, and showed that the supposed pellagra of the sanatorium for the insane just mentioned, as well as that at Auxerre, was really nothing more than barber's itch.

A perusal of the older literature on this subject shows hardly anything more than that the patient was sick, and that he either suffered from some sort of skin trouble or had a diarrhoea. It would be profitless to insert at this point a record of even a few of these cases, since the lack of accuracy of description characterizes them all, and nothing could be gained as a consequence.

Of the more recent cases the same criticism would be on the whole not unfair; while it is true that writers are now somewhat more careful in their description of details, it is noteworthy that those reporting these conditions appear still to have but the vaguest conception of the true and peculiar characteristics of the pellagrous manifestations, and that while they may use a greater number of words than their predecessors they have in effect said little or nothing more. As undoubted examples of more or less common conditions being mistaken for pellagra are a number of cases that have been reported from England during the last few years,—in the clinical descriptions of which a number of irregular and atypical skin and nervous manifestations are mentioned, which bear clear internal evidence of having nothing whatever to do with pellagra.

Lastly it is of the greatest importance to observe that Thomas has recently called attention to the fact that typical pellagrous erup-

tions often follow the administration of sulphonal in ordinary doses, and as this drug is freely used in all sanatoria for the insane there can be little doubt that it has been frequently the cause of supposed cases of pellagra in patients at such institutions.

After the foregoing remarks the author feels that nothing could be gained by pursuing the subject further, and he will dismiss this phase of a very complex problem by saying that any skin disease occurring on the face, hands or feet appears likely to be regarded as pellagra; that divers nervous diseases, particularly if they are at any time accompanied by an erythema, are likely to be mistaken for this disease, and that where a patient likewise presents evidence of a psychosis the error is almost certain to occur should he fall into the hands of the pseudo-pellagrologists.

Cereal intoxications.

Inasmuch as it is generally conceded by those best entitled to an opinion that pellagra is associated with the consumption of bad maize, it would be only natural to assume that other affections produced by cereals should show a certain degree of resemblance in their clinical manifestations to those observed in this disease, and a perusal of the literature on this subject shows beyond doubt that this assumption is sustained by the facts in the case. Indeed it may be said that there is a very striking similarity between the effects produced by the consumption of cereals that have undergone alteration and those observed in this affection, so that Rayer is fully justified in saying, at least as regards the malady produced by bad wheat, that "the differences between it and pellagra are much less marked than the resemblances."

In all of these diseases, following a certain period of disturbances of the nervous system, symptoms referable to the skin and intestine develop, and in all of them there quickly occurs an extreme degree of asthenia, followed by pareses or paralytic conditions, and a profound cachexia, and not infrequently the melancholy picture terminates in insanity.

However, in such cases the history, and a careful attention to detail should make the diagnosis clear.

Ergotism.—As is well-known, ergotism is the result of the consumption of rye in which the ergot fungus has developed,—a fungus which it should be well to remember is closely related botanically to the moulds that produce poisons in maize. In this disease skin alterations have been frequently observed, not uncommonly associated with swelling of the hands and feet, and in addition there may form numerous vesicles, followed by erosions.

Diarrhoeas are also frequent, and the patients not uncommonly exhibit bulemia.

Spasms, either of a tonic or clonic character, are extremely common, and are more marked in every way than in pellagra. Likewise formication is not uncommon, and has been in some epidemics sufficiently pronounced to give the disease in Germany the name of "Kriebelkrankheit." In some instances these patients present coreai-

form movements or epileptiform convulsions, and occasionally opisthotonus occurs. Likewise some patients exhibit strabismus, convulsions of the face, and difficulty in articulation.

On the other hand the victims of this malady rarely suffer from pyrosis or cardialgia. Neither stomatitis nor vertigo appear to occur. The erythemas are not limited to those situations in which they are found in pellagra.

In both ergotism and pellagra insanity may finally result, but it appears to be much more common in the latter.

Acrodynia.—Acrodynia is a condition which is believed to be the result of the consumption of fermented wheat.

Skin symptoms occur likewise in this disease, there being an erythema, with redness, accompanied by a swelling which commonly occupies the palmar and plantar surfaces, often making its way up on the sides of and completely encircling the hands or feet; these changes resemble rather more a violent urticaria than a typical erythema.

There is likewise a burning sensation in the parts of the skin affected, which is particularly painful during the night. This is quickly followed by disturbances in tactile sensibility. There are likewise not infrequently present itchings, a dead feeling, tingling, and particularly a pricking sensation, which extends along the length of the hands and feet. Chardon has observed convulsive movements, and even symptoms resembling tetany, though such phenomena are much less common than in ergotism, or even than in pellagra. This is sometimes followed by contractures, subsultus, and lack or coördination in movement.

In the earliest stages of the disease there is marked insenibsility, which is later replaced by hyperaesthesia, both superficial and profound.

As the patient approaches the latter stages of the disease the epiderm peels off of the diseased areas, forming large scales, such as are observed in scarlet fever, and leaving the skin almost of a black color.

During the period of convalescence, which varies from five to six months, the patient gradually gains strength, and as a rule recovers.

In the third stage of the disease inflammations of the conjunctivae are common, according to Rochette.

It is said by Rue that this disease usually comes on at the end of the winter, generally occurring in May or June.

Rochette affirms that fever is not uncommon in the earlier stages of the malady, but that it does not occur after the acute period is passed.

Clairat and Miramond have each reported cases with the usual symptoms, and Cole has reported three cases in this country which he thought might be instances of this affection, but his description was so brief that some doubt remains as to their true character.

From the foregoing it will be seen that acrodynia presents many characteristics in common with pellagra. Inasmuch as this affection

is apparently very rare, and usually occurs in epidemics, that it is not preceded by years of maize eating, that the eruption occurs on the palms of the hands and the soles of the feet with coarse scaling later, that there is a pronounced conjunctivitis and swelling of the eyelids in the third stage of the disease, that during this period there is no fever, and that the attacks are much more prolonged, a diagnosis between the two conditions should not be a matter of difficulty. It may be further mentioned that mental changes do not appear to occur in acrodynia.

Lathyrismus.—Lathyrismus is a disease which has long been recognized as the effect of the consumption of various members of the pea or bean family.

As to just what conditions are necessary for the production of this malady writers seem to be in doubt. It is believed by some that the simple consumption of excessive quantities of beans, particularly where the hulls are eaten, ultimately leads to its development, while still others have assumed that fermentative changes are necessary in order for the poison to be elaborated.

It is stated by Lavello that a disease occurs in Basilicata, that closely resembles lathyrismus, which results from eating peas; this malady is very fatal and comes on only in the spring and summer. A similar affection has been described by Camillis in Sicily.

Astier, working among the Arabs in northern Africa, has written a most excellent paper on lathyrismus. It appears to occur much more frequentin in men than women, and seems to develop almost always after the body has been chilled.

The malady comes on suddenly, the patient very often finding in the morning that he is unable to get up, and the effort to do so is followed by trembling, which is quickly transmitted to the entire body. Not uncommonly there is pain around the waist, or constriction about the belly, accompanied by uncomfortable sensations in the legs, and ultimately ataxia. The pains do not as a rule occur above the umbilicus, and usually disappear after a few weeks. Curiously the trouble is said to begin usually on the left side and to be more pronounced here than on the right. There are present in the legs hyperaesthesia, tinglings, prickings, and a sense of heat or cold, followed by anaesthesia, which is always more marked on the anterior surface of the limb; in rare instances sensibility is not affected.

In some cases the lesion would seem to indicate a transverse myelitis, while in others the symptoms are those of tabes; most commonly the patient appears to suffer from a typical lateral sclerosis.

The sphincters are seldom affected. The sexual sense is much excited in the beginning, but entirely ceases during the course of the disease and never returns; it is quite remarkable that many of the patients largely recover in other ways, but remain impotent.

From the foregoing it is seen that this affection is clearly one of the nervous system, and in this particular resembles pellagra; further it may be said that both have many symptoms in common, but, in addition to the history, the differences are so marked that a mistake

in diagnosis would not be likely except in the last stages of the disease, where the condition is practically the same as that seen now and then in pellagra at its termination.

It is said by Kirk that the malady is much more common in some districts than in others, and that only a comparatively few people suffer, even where the disease is most prevalent. He particularly stresses the great differences in susceptibility of different individuals.

Beri-beri.—Notwithstanding the fact that it was long ago apparent to acute observers that beri-beri or kakke is associated in some way with the eating of rice, it has only been within comparatively recent times that a better understanding of this subject has been arrived at, thanks mainly to the investigations of Eyckman. As is now well-known, it has been proved that this malady results from the removal from the cereal during its preparation for the table of certain principles necessary for life, called by Funk "vitamines," and that where the human being attempts to subsist wholly on grain with this life-giving substance absent, beri-beri develops. However, it would seem that there is still some factor in the causation of this affection which is not yet understood.

The symptomatology of this disease is so unlike that of pellagra that a comparison of their clinical phenomena scarcely seems necessary. It is, however, worthy of note that in this cereal disease the lesions are largely confined to the nervous system, a peculiarity that characterizes them throughout. In beri-beri the principal diagnostic symptom is the presence of a general neuritis, with edema in various parts of the body, a condition accompanied by such intolerable suffering that a mistake in diagnosis could scarcely occur.

It is well-known, as mentioned by Scheube, that patients suffering from beri-beri occasionally develop erythemas, but neither in location nor clinical course do they simulate pellagra. Wilson has recently reported a case of supposed beri-beri in which the patient had an erythema on the backs of the hands much like that seen in pellagra, but the diagnosis was not beyond question, and likewise the victim may have suffered from a concurrent pellagra.

Saunders, of South Carolina, has recently reported cases where pellagra and beri-beri were supposed to have existed simultaneously. It may however be doubted if her conjecture be correct, in view of the improbability of patients in this country suffering from vitamine hunger, and of the occasional association of neuritis and edema with pellagra.

Darnel intoxication.—It is said that the intoxication that results from the consumption of bread into the composition of which darnel flour enters produces in the consumer intense vertigo and a feeling of drunkenness. Very curiously it has been apparently proved by Tozzetti that the mature darnel furnishes a wholesome flour and may be eaten without ill effects; it is only the unripe seeds that appear to be poisonous. This intoxication is accompanied by an intense headache, terminating sometimes in delirium and even death.

Where the patient recovers there persists a marked feebleness, and even a condition approaching paralysis for a considerable time.

It does not appear that this substance produces either skin or intestinal symptoms.

Other forms of intoxication.—In addition to the cereal poisons, it is unquestionably true that narcotic drugs, such as sulphonal, opium, hasheesh, belladonna, mushrooms, shumac, etc., may give rise to pellagroid manifestations, as may also the metallic poisons, such as mercury and arsenic, but it is hardly necessary to take up the reader's time with a full discussion of the peculiar states produced by each. Mistakes in diagnosis of this character are extremely unlikely, and could rarely or never occur where the possibility of such a result is recognized.

Rheumatism.—While pellagra and rheumatism present little in common, attention should be drawn to the fact that pains in the limbs and joints is not uncommon in the former, and that mistakes might possibly occur in cases without the characteristic eruption and dyspeptic symptoms. It is only necessary to speak of the possibility in order to avoid the probability of errors occurring.

Sunburn.—Notwithstanding the fact that the circumstances attending the development of the skin lesions of pellagra and sunburn vary widely, and that the two lesions differ from each other in their course and symptomatology, an apparent relationship in the method of their production has created the confusion which it appears no aspect of this subject can be permitted to escape.

Since the time of Gherardini it has been known that pellagrous lesions may be developed in proper subjects by simple exposure to the sun, but whether or not we should regard the dermal changes that follow as belonging to this disease or simply as a sunburn has never yet been satisfactorily determined. That pellagrins are peculiarly prone to inflammatory disturbances of the skin following exposure to sunlight and other irritating agencies, there can be no question, and the author is personally of the opinion that in the spring typical pellagrous onsets may be precipitated by such influences, and that they may even determine at this time an attack which might have been avoided under happier conditions. However, a careful clinical study of cases of this kind is much to be desired, as it is only in this way possible to settle the question definitely. It may be said in this connection that Merk (2), who is one of the greatest authorities on this subject, is decidedly of the opinion that such cases should always be regarded simply as sunburn, and that they consequently have nothing whatever to do with pellagra.

That the pellagrous lesions and sunburn closely resemble each other both at the beginning and end of these pathological processes cannot be questioned, but in other particulars the changes vary widely.

Sunburn is of course always associated immediately preceding the outbreak with exposure for a greater or less length of time to the

direct rays of the sun, and is naturally situated, as a rule, on those parts of the body where the pellagrous lesions usually appear; it should however be remembered that in pellagra not infrequently the parts of the body later affected are covered, and dermal lesions in such situations would at once settle the diagnosis. It is furthermore true that the lesions of sunburn pursue a very much shorter course than do those of pellagra, and instead of the exfoliation occurring in the form of fine scales of a grayish color, beginning in the central portion of the lesion and extending outward, we have here the simultaneous shedding off of the epiderm over the entire diseased surface—it sometimes coming away *en masse*—and presenting a whitish or whitish-yellow color. It is of course true that the changes in sunburn rapidly disappear, never persisting as is the case with the pellagrous lesions. It may likewise be mentioned that the intensity of the solar erythema is usually by no means so great as that of pellagra, and that the color of the lesion is always bright red, contrasting sharply with the blue, lead-like appearance which is so quickly assumed by the skin in the latter malady. Inasmuch as the intensity of the changes produced by the sun is much less than is the case with pellagra, we do not have, as so often occurs in the latter affection, the formation of blebs or cracks in the derma.

The reader should be particularly warned against the very common error of mistaking for pellagraderms the sunburns that occur in alcoholics, in the insane, and in those who are the subjects of chronic cachexias. The resistance of their tissues being low, the victims of such conditions are extremely prone to sunburn, and there can be no question that a great many of the reported cases of parapellagra originated in this way.

Vitiligo.—The lesions of vitiligo, which not uncommonly become aggravated in the spring, sometimes show such a close resemblance to those of pellagra that mistakes are extremely likely without great care is exercised. In this affection the lesions may likewise affect the backs of the hands, and even present a livid appearance surrounded by a pigmented area that fades away insensibly into the surrounding skin. On close examination however it is found that the surface is smooth and does not present the scaling that is inseparable from the latter stages of the pellagrous lesions. Furthermore it is true that the changes encountered in this disease are never confined wholly to the hands, and in all cases where doubt exists the entire body of the patient should be examined. It is likewise the case that in vitiligo the skin alterations are usually found to be of many years duration, and do not present the well defined series of changes, lasting from a month to six weeks, which are observed in pellagra.

Eczema.—In making the differential diagnosis between eczema and pellagra it should first be observed that it is only cases of the former, where the lesion appears on the hands, face, neck and feet, that could be mistaken for the latter; it is furthermore true that in pellagra the changes practically always appear on the hands at about

the same period that they occur on other parts of the body, and, as this rarely or never happens in eczema, it may be affirmed that mistakes are really only likely where the lesions of this nature are wholly confined to the backs of the hands. Under such circumstances the diagnosis may nearly always be settled by remembering that the pellagrous lesions are invariably preceded by the minor manifestations to which attention has been so frequently directed in these pages, and that in order to simulate the true pellagraderms eczematous changes must quickly assume a squamous state, with sharply defined boundaries; in addition itching must not occur, and the malady must not pass through a vesicular stage; finally the scales must be gray and of rectangular form, and the corium must at this stage show complete absence of inflammatory change. In addition it may be noted that eczematous disturbances are usually quickly influenced by treatment, in which they sharply differentiate themselves from pellagraderms.

Papular erythema.—The author has recently seen a case where a papular erythema, in a diabetic, was mistaken for a pellagraderm; while the lesions were confined to the backs of the hands and the first phalanges, they presented a papular appearance, totally unlike the smooth, uniformly dark-red lesions of pellagra. Furthermore the papules, while varying greatly from day to day, had persisted for months. Still more recently another case was seen, in an otherwise healthy person, the lesions being sharply confined to the back of the hands and fingers.

Erythema exudativum multiforme (Hebra).—Pellagra and *erythema exudativum multiforme* present many characteristics in common, and there can be little doubt that many of the so-called cases of sporadic pellagra were in reality examples of the latter affection.

To begin with it is well-known that Hebra's disease has a marked tendency—so often observed in skin affections—to appear in March and April or October and November,—though it is by no means always the case that these months are selected.

The actual lesion in this malady invariably affects the backs of the hands and feet, and in its severer forms, like pellagra, it may appear on the forearm and leg, or upper arm and thigh, and in rare instances may spread to the face and body; likewise—and in this it again resembles pellagra—when it appears on other parts of the body the disease usually first manifests itself on the backs of the hands. The lesion does not burn, nor is there objective evidence of increased temperature. Notwithstanding the close resemblance that the two maladies present, the skin lesions are not identical, there being something in the erythema of pellagra that distinguishes it with more or less certainty. The typical arrangement of the lesions in the latter disease, the sharply defined borders, the peculiar character of the skin lesions, with their regular succession of changes, are not exactly simulated by Hebra's disease. The scales in pellagra are small and rectangular, and occur with considerable uniformity over the surface, undergoing desquamation, while in *erythema exudativum multiforme*

the exfoliated epithelium comes off in large lamellae, giving to the surface a ragged appearance.

Attention must be here called to the great differences in the general symptoms encountered during the erythematous stages of the two diseases,—the pellagrin showing invariably to a greater or less extent the peculiar mental and physical disturbances, which, particularly when presenting themselves in the spring, are most characteristic.

Parasitic diseases of the skin.—As is abundantly shown by the experience of the past, parasitic diseases of the skin have furnished a not inconsiderable proportion of the cases of so-called sporadic pellagra, barber's itch and ringworm appearing to have been the chief sources of error.

It is hardly necessary to go into a detailed description of the points of differential diagnosis, since a warning of the possibility of mistake should be quite sufficient to prevent its occurrence. The peculiar, localized but slowly spreading character of the lesions, coupled with their persistence month after month practically unchanged, without systemic symptoms, should always make the diagnosis clear,—and where doubt still exists a microscopic examination would always settle any uncertainty beyond question.

DISEASES OF THE DIGESTIVE TRACT.

While generally speaking the gastrointestinal disturbances that occur in pellagra may be differentiated from kindred conditions with ease under ordinary conditions, it is true that in instances where the mouth, stomach or intestinal disorders constitute for the time being the sole or principal manifestations errors in diagnosis are not impossible.

Mouth.—In rare instances it would appear that the only objective symptom associated with pellagra consists in changes in the mouth. Under such circumstances, in addition to the minor pellagrous symptoms, which, as so often reiterated, are always present, there may be simply a chronic inflammatory condition of the tongue, associated with lobulation of its surface, brought about by the presence of numerous furrows or, by actual cracks in the mucosa accompanied by painful inflammatory change; under such circumstances there are usually also grayish streaks representing the scar formation beneath the surface, patches of leucoplakia, and scattered here and there areas over which the epithelium has apparently entirely disappeared, leaving the surface slick and glassy. Around the gums, on the buccal mucous membrane, and in the throat there may be also the peculiar livid appearance which is so characteristic in the chronic stages of this malady. In contrast with the lesions just described are those encountered in scurvy, a disease fortunately at the present day so rare in the adult that it may be said to have practically ceased to exist; here the lesions are largely confined to the gums, are associated with hemorrhage, and present a wine colored appearance.

The lesions observed in syphilis might also be mistaken for those of pellagra, though a careful examination will reveal that the peculiar appearances just referred to are not simulated by this malady; in addition we would of course have the constitutional symptoms, the peculiar skin eruption, and the enlarged lymphnodes to assist in differentiating the two affections.

Mercurial salivation may also present symptoms which somewhat remind us of those of pellagra; here again, however, when we keep in mind the characteristic mouth changes there is but little danger of errors in diagnosis; it is true that in both conditions ptyalism may occur, but it is rarely in pellagra so pronounced as in mercurial poisoning, nor is it associated with the peculiar and characteristic odor of this pathologic state.

Stomach.—Now and then it occurs that the principal and most manifest of the pellagrous symptoms confine themselves to intestinal disturbances which may resemble the common forms of dyspepsia, and, where pain occurs, might even arouse the suspicion of cancer—particularly as the patient under such circumstances usually rapidly loses flesh and becomes anaemic, and frequently sinks into a condition of cachexia that might at first glance somewhat resemble that brought about by malignant disease.

Under such circumstances we will have to depend on the general symptoms presented by pellagra and those of the condition suspected in order to make the diagnosis clear.

Since the commonest form of indigestion in America, at least, is associated with increased acidity, and the hydrochloric acid is greatly decreased or absent in pellagra, a stomach analysis may often be of value in arriving at the true solution in cases that are not clear; on the other hand the condition of the gastric juice is usually the same in chronic pellagra and carcinoma; under such circumstances the peculiar lobulation of the tongue and the chronicity of the process, along with the minor symptoms of the first stage of pellagra, should be quite sufficient to clear up the diagnosis.

Intestines.—As is well-known, the pellagrous onset is frequently accompanied by diarrhoea, which may at times assume the characteristics that distinguish an ilio-colitis. As a general rule however, even in the acute stages of the malady, the stools rarely contain blood or mucus, nor are these substances found in the evacuations of the more chronic forms of diarrhoea, which occasionally last for years in old pellagrins. Under such circumstances a differential diagnosis will have to rest on the general symptoms,—and as these have usually included at some time either wholly or in part the major and minor manifestations of this malady, it is not as a rule a matter of great difficulty to make the diagnosis.

The author has more than once seen instances of amoebic dysentery mistaken for pellagra; for such an error however there is little justification, as, in addition to the microscopic examination of the stools, the markedly dysenteric character of the symptomatology of this malady is in sharp contrast to that of pellagra.

Sprue.—For many years the author has been in a state of grave doubt as to whether or not the disease called sprue—at least in America—is after all in reality nothing more than a chronic intestinal type of pellagra. For some ten or twelve years he has occasionally encountered cases that presented all of the classical peculiarities of sprue, and as such they were long regarded, but with a better understanding of the possibilities of pellagra considerable doubt has arisen in his mind as to the correctness of his former conclusions. While it is true that maize is a common article of diet in those parts of the world where sprue is most frequent, the apparent absence in these regions of typical pellagra would seem to point strongly toward the non-identity of the two affections; it is possible under such circumstances that maize is not eaten in sufficient quantities to produce a pronounced state of maidismus, though at the same time enough is consumed to occasion intestinal disturbances. While in some of his cases of supposed sprue there was a history of the diarrhoea being particularly marked in the early morning hours, the author never succeeded in entirely convincing himself that these manifestations were of that peculiar nature that characterize the diarrhoea of sprue, nor were the stools ever of that light color and voluminous character that all authors agree is common in this malady. Lastly it may be observed that sprue may occur in young and healthy people, who afterwards entirely recover,—the author knowing of one instance where the patient has remained well since the Spanish-American war.

All these considerations then lead the author to doubt strongly that pellagra and sprue are really identical, though unquestionably the subject needs careful investigation.

Manning has recently written an interesting paper in which he has suggested that the "psilosis pigmentosa," of Barbados, is really pellagra; after carefully reading his paper the author has no hesitation in saying that this form of sprue differs in many ways from pellagra.

The identity of these two affections has recently been urged by Stewart, but as this writer has probably had no extensive acquaintance with both diseases his conclusions could scarcely be more than theoretical deductions, the possibility of the correctness of which, however, cannot be gainsaid.

In differentiating the two affections it should be remembered that sprue resembles pellagra only in the presence of a sore mouth, and in diarrhoea; we do not meet with skin lesions, nor are there the characteristic nervous and mental symptoms; furthermore there is no tendency to seasonal exacerbations, continued for long periods. It is therefore only possible to err in those cases where the pellagrous lesions are chronic and are confined to the digestive tract. Lastly, there is no evidence that sprue shows any tendency to heredity.

Psychoses.—As has been already indicated, authorities are not in agreement as to the precise nature of the mental changes that occur in pellagra, and we are therefore not in a position to

differentiate definitely the mental states occurring in this malady from psychoses that develop from other causes.

It can only be said that to the layman pellagrous mental alienation appears to consist in a profound melancholy, combined with mutism, a sluggish state of the mind, and a marked disinclination to mental and physical exertion, combined with which some authors assert there is a tendency to suicide, though it appears that in the past this disposition has been much overstated. It is likewise noteworthy that when patients are repeatedly appealed to they not uncommonly show a degree of intelligence greatly in excess of what would be supposed to exist on a cursory examination,—a peculiarity which Vedrani has recently regarded as being characteristic of the pellagrous psychoses.

According to some authors it would appear likewise to be the case that amentia, dementia, mania, melancholia, delirium, etc., are occasional or even constant symptoms of pellagrous psychoses, but in how far the apparent frequency of such conditions is the result of error cannot be said; it is certain that in many instances of supposed pellagra the patients belonged to that decidedly uncertain group known as "pellagra of the insane," and it is unquestionably true that many victims of the former malady have been thought to be in a state of complete amentia, who, on close questioning, would have revealed the error of this view.

It is obvious where such a state of affairs as this exists that it is a waste of time to attempt a differentiation between pellagrous psychoses and insanities from other causes. It can only be urged and hoped that this subject will be taken up by some competent observer with undoubtedly pellagrous cases and his studies continued until some satisfactory solution is arrived at.

Cachexia and the atypical types of the third stage.

To attempt to differentiate the clinical types exhibited by the victims of advanced pellagra from similar pathologic states unassociated with this malady would be an almost endless task, and would enlarge the scope of this work to a degree entirely out of proportion to the importance of the subject. Suffice it to say that in the latter stages of this disease practically every organ and tissue of the body undergoes pathologic alteration, and that the symptomatology of any and all diseases produced by general intoxications may be not infrequently simulated. Among the more common clinical types that occur under such circumstances are acidosis, chronic gastroenteritis, amyotrophic lateral sclerosis, tetany, pseudo-meningitis, insanity, essential anaemia, chronic degeneration and atrophy of the various organs, Addison's disease, paralysis agitans, thyroid disturbances, and finally the so-called typhoid pellagra, in which, however, the patient presents rather the symptomatology of *delirium tremens*. In addition there also occur various physical anomalies the result of improper development in the offspring of pellagrins, and likewise a weakened constitution and stigmata of degeneration. Lastly it should not be forgotten that any

and all of these symptoms may occur without the development of skin lesions.

In instances where we are in doubt as to the diagnosis it can only be insisted that here, as in the more characteristic types, a solution of the problem must largely depend on the patient's history, and particularly on the occurrence of the minor pellagrous symptoms, on the changes in the tongue and mouth, in combination or not, as the case may be, with some of the major manifestations. Where the history is carefully gone into and the patient afterwards thoroughly examined, it is perhaps true that in the great majority of instances a diagnosis can be made with a fair degree of certainty.

CHAPTER VI

PROGNOSIS.

The prognosis where pellagra has fully developed, like that of other diseases associated with anatomic lesions, is by no means good. This fact in itself is weighty evidence of the author's thesis that the ordinary pellagrous symptoms have but little directly to do with intoxication from maize, and that probably they are directly or indirectly solely the result of morbid alterations of the internal organs —more particularly of the central nervous system; however, the foregoing statement respecting the prognosis applies more particularly to the malady occurring in adults after one or more of the major manifestations that characterize it have made their appearance, and does not include the neurasthenic phase of the disease—at least so far as immediate danger to life is concerned. We then see that in arriving at a conclusion as to the fate of a given case of pellagra we must largely depend on the severity of the symptoms, althought unfortunately they do not by any means always afford us satisfactory guidance.

It would appear likewise that the age of the patient materially influences the prognosis, as it seems quite certain, at least so far as life is concerned, that the malady is rarely fatal before maturity, even where the patient has exhibited all of the classic symptoms of the disease. While under such circumstances all major symptoms often subside, and the patient apparently returns to a normal condition, the author gravely doubts if in any instance recovery ever really occurs. It is a matter of every day experience that one or more of the outbreaks—even where the major manifestations are severe—may be triumphantly overcome in youth, or even in later life, but it seems in the highest degree probable that the organic changes upon which the clinical manifestations likely depend are of such character that in the very nature of things a complete restoration to the normal is impossible, and that it is only a matter of time until the symptoms will recur. Indeed it appears to the author highly probable that the melancholy aphorism of Verga to the effect that "pellagra never goes backward in its course" is essentially true, and that in reality, when the disease is once begun, that changes, particularly in the nerve cells, probably continue throughout life. Nor does it appear after the process is once initiated that the peculiar poisons giving rise to it are longer absolutely essential, though it seems probable that in their

absence the pathological process likely proceeds much more slowly. As particularly emphasized by Kozowsky the lesions of pellagra resemble most closely those of senility, and since the pathologic changes associated with old age are generally thought to be toxic in origin, there appears no reason, *a priori,* why the more or less altered and weakened nerve tissues of the former should not be in a special degree susceptible to the deleterious influences connected with the latter. It is then the view of the author that pellagrous conditions once initiated are probably gradually increased with time as a result of the autointoxications from which we perhaps all more or less suffer, and that whenever the vitality is sufficiently lowered external manifestations of the malady occur.

The rapidity with which serious disturbances of the bodily functions occur is doubtless directly proportionate to the degree of alteration in the sympathetic and central nervous systems, and, in cases where the malady is recognized very early and the proper precautions taken, it is not improbable that the patient might live out his days, or die but little earlier than would have been the case under normal circumstances.

In other instances, where the diagnosis is not made so early, or where the patient does not entirely cease eating maize, or fails to conserve his health in a proper manner, death may occur earlier, being brought about by a major attack of pellagra, or indirectly by weakening the body and causing it to become the easy prey of some intercurrent disease.

In cases where the affection is not diagnosticated until a classical attack of the disease has occurred, the prognosis is good as concerns the first two or three outbreaks, particularly if the patient be young; on the other hand the chances of an ultimate recovery are *nil,* as the patient will surely come down with succeeding attacks sooner or later, and if not carried off by some other disease in the meantime will in the end succumb to pellagra.

It is thus seen that like everything else connected with this remarkable affection the *prognosis is exceedingly uncertain and depends upon so many factors—some of which are always unknown—that we can never form beforehand any very intelligent opinion as to the probable outcome of any given case.* We can only say that if the *disease is mild* and the *patient is young* the chances of recovery from the immediate attack are *good,* while the *opposite is true under contrary conditions.*

As regards the prognostic value of the individual symptoms it may be said that generally speaking the amount and degree of the *skin lesions bear no close correspondence to the severity of the attack,* a fact insisted upon by Strambio, but where they are *atypically located the disease is almost always severe.* Where, moreover, there are *marked intestinal disturbances, with much denudation of the mucosa of the mouth, the prognosis is not so good,* and in instances where we have *in addition pronounced mental change, the chances of the patient are still further worsened.* The most violent forms of pellagra seen by the author have been instances in which the major symptoms were

initiated by the sudden collapse of the intellect, preceding the other classical symptoms.

Devoto says the prognosis is good in old persons becoming pellagrous.

The results of clinical experience show that the prognosis in children is quite uniformly good.

Where no marked eye symptoms occur the disease is rarely severe.

The prognosis is bad where the alkalinity of the blood is markedly diminished.

Probably the most favorable of all general symptoms is absence of fever.

As regards the atypical forms of this disease no general rules as to the prognosis apply; such cases are likely to be exceedingly chronic, with the exception only of those developing acidosis, which not uncommonly occurs as an independent pellagrous symptom-complex, and which are frequently fatal.

From the foregoing it is seen that we can never, as long as life lasts, speak a final word as to the prognosis in pellagra; cases die where we have every reason to think recovery should occur, and others come back to life, and even fairly good health for years, from the very brink of the grave. The only thing we can say with certainty as to the prognosis is that the disease will certainly recur sooner or later if the patient does not die of some intercurrent affection, and that each case must rest on its individual merits.

It is said that cases of typhoid pellagra sometimes recover, but such an occurrence is very rare.

CHAPTER VII

PROPHYLAXIS.

The measures best calculated to prevent the occurrence of pellagra should naturally be those that are directed toward keeping the causative agent out of the human body, but since it must be admitted that absolute and final proof of the etiologic factors in this malady is still wanting, it cannot be said that we are in a position to formulate definitely the proper prophylactic procedures.

On the other hand it cannot be denied that there is abundant evidence going to show that the disease is the result of the consumption of mouldy maize, and that experimental investigation has strengthened this view until there can be no longer any reasonable doubt as to its truth. Furthermore it may be said without fear of contradiction that the evidence of this relationship is even much stronger than is the supposed etiologic connection between a number of diseases and their supposed causative factors, and that to any one acquainted with all of the facts an attempt to discredit the maize theory appears almost certainly doomed to complete failure.

The author would however quite agree with the old French writers Bouchardat and Tardieu, who maintained that if moulds are capable of producing the pellagrous poisons when growing on maize starch, there can be no reason why this might not occur when they develop on starchy substances from other sources, and that it is possible for pellagra to result from the consumption of bad breads made from wheat, rye, barley, etc. More recently this view has again been put forward by Gosio, who quite properly says that it is probable that it would be more correct to speak of pellagra as being a *mould poisoning* than a *maize poisoning*. This view receives confirmation in the work of Peglion, who has found that moulds frequently develop in chestnuts, with the production of their characteristic poisons—which quite likely accounts for the occurrence of pellagra in those districts where it is said but little maize is consumed, but where the inhabitants live largely on chestnuts. It is only maintained therefore by the best authorities that maize consumption is the common and by far the most frequent cause of pellagra, and this is the result simply of the fact that this cereal becomes mouldy much more frequently than do the others commonly employed as foods.

The author then has no hesitation in saying that he is in entire accord with those who hold that the consumption of maize is responsible for the production of this disease, and is therefore of the opinion that our only hope of getting rid of it is inextricably connected with the abandonment of Indian corn as a food. In certain particulars he is inclined to go a step further than have previous writers on this subject, believing that the affection *is nearly if not always the result of the habitual use of maize as a food by the ancestors of its victims.* As stated in the chapter on causation, the view has widely prevailed since the days of Albera that pellagra is hereditary, an opinion that has grown with our increasing knowledge, and which may be said now to be universal among all real students of the affection. Influences of this kind have not, however, been regarded in the past as of the first importance, it having been held at most that the disease is only hereditary in a certain proportion of cases. It has furthermore been accepted by the advocates of the maize theory that the acute manifestations of this disease are intimately connected with poisoning by maize immediately preceding their outbreak,—a view which is substantiated by undoubted instances of acute poisoning from bad maize both in the human being and in experiments on animals. In the opinion of the author this conception has been one of the most fruitful sources of error in a proper understanding of pellagrous processes, and has given rise to the principal objections that have been heretofore urged against the maize theory. To him it seems all but certain that such manifestations really have no connection whatever with pellagra, and that in reality this affection always represents the reaction of the organism to intoxications of an extremely chronic character, and, still more, to pathologic change in the organs of the body. That it is absolutely essential in order that the disease may be produced that the immediate ancestors of its victims must have been maize eaters the author would not venture to assert, but he believes that future observation will probably show that such influences are always necessary.

According then to the author's opinion pellagra is a disease which is a remote result of an intoxication from eating Indian corn, that develops only in the offspring of maize eaters in all or in a great majority of instances, but which may possibly occur in others as a consequence of the continued use of the products of bad maize extending over a long term of years.

If we assume the correctness of the foregoing views, it would appear that in order to prevent this disease in the future the consumption of maize must be greatly restricted or abandoned altogether, and *that we cannot expect a complete cessation of the malady until at least one generation has passed following the institution of such measures.* We should furthermore remember that where no such hereditary influences exist it is conceivable that the organic changes characteristic of this disease may be brought about by eating products of Indian corn for a number of years, but it should be recalled that where the damage has already been done the aban-

donment of the use of this cereal cannot be followed by a restitution to the normal, and that such persons would probably be liable, whenever their vitality is lowered, to acute outbreaks of typical pellagrous symptoms as long as life lasts. Where an ancestral taint is combined with the habitual consumption of maize the pathological changes must of necessity be of a still more pronounced and widespread character, and it is doubtess this class of cases that furnish us with the great majority of typical pellagrins.

It seems then not unreasonable to assume that we have a double problem in connection with the prevention of pellagra: first and foremost we should attempt to prevent normal people from becoming pellagrous by either prohibiting altogether the use of maize, or so restricting its use as to avoid anything like a pronounced intoxication; secondly we should attempt to prevent the affection from becoming aggravated in those in whom it has commenced, both by forbidding absolutely the use of maize products, and by the use of appropriate measures for keeping the victim's general vitality as near the normal as is possible.

In this chapter it will only be necessary to consider the prophylactic measures connected with the use of Indian corn as a food, since the procedures associated with the prevention of succeeding pellagrous attacks in those who have once suffered from the disease is more naturally included under the head of treatment.

If it be granted that the generally accepted theory of the production of pellagra is correct, nothing could be simpler in theory than the complete abolition of the disease, and it would only be necessary for us to advise that no more Indian corn be eaten. Unfortunately, however, the practical difficulties in the way of carrying out such a measure are very great; indeed, obstacles in the way are of such character that we may at once assume that it will probably never be possible to bring this about, and we are therefore forced to advise such other precautions as would appear to be most likely in the present state of knowledge to produce good results.

While it is admitted that the zein of maize is far from being wholesome, and that ferments of a more or less deleterious character occur in this grain, it is not at present generally thought that the inherent bad properties of Indian corn are responsible for the greater proportion of the ill effects incident to its use. On the other hand it is known that this cereal almost always becomes more or less mouldy before being eaten, and that under such circumstances poisons are produced that may give rise to pellagra; our preventive measures then should be largely aimed at limiting as far as possible the habitual eating of mouldy maize, and it is with this idea in view that the following measures are advised.

(1) *Cultivation of the best varieties of maize.*—The maize genus comprises but a single known species, *Zea Mays* Linn. Of the ten known varieties only five are cultivated for their grain, these being known respectively as *flint, dent, flour, sugar,* and *pop-corn;* these are further subdivided into a large number of subvarieties or breeds.

Unfortunately it is not possible to assert categorically that this or that variety of maize is the best under all conditions and under all circumstances.

It may, however, be affirmed that with proper care fairly safe breeds of this cereal may probably be found for all climates where the plant develops sufficiently to be used as food. Unfortunately this subject has not been studied to a sufficient degree to enable us to formulate any general rules in the matter. To begin with it does not appear to have been definitely determined as to which of the five main varieties is the most wholesome. As indicated in the chapter on causation, pellagra is not thought by the best authorities to be dependent on the toxic substances naturally present in the grain, but is the result of the formation of poisons in the cereal as a consequence of the action of moulds. In selecting a corn then for any particular locality it should be our endeavor to determine what variety is least attacked by these parasitic organisms. This matter has been given some consideration by Italian investigators, but the results appear, unfortunately, on the surface to be somewhat contradictory. Thus it is stated by Brizi, Gosio (9), Colloidi and Frosini that in Italy the most resistant variety of maize is what is known as the *red cuzco*, while the *white cuzco* and *black friulano* are almost as refractory; of a medium susceptibility is the *agostano* and the *yellow quarantino*, while the *white caragua*, the *yellow semplalatore*, the *cinquantino*, and the *cento giorni* permit the growth of the hyphomycetes with the greatest facility; of these the worst happens to be the *cinquantino*, which according to Gosio is infected in 90% of cases. Sanarelli (1) has recently demanded that laws be passed that would prohibit the cultivation of *cinquantino*, and *quarantino* in Italy. Unfortunately none of the Italian writers give any information as to which of the five great varieties now recognized by botanists these different breeds belong. It is true that Morelli attempted a classification, but this was based on the color of the grain, a characteristic not now employed for this purpose. The only light that the author has succeeded in getting on this subject is that that comes from a letter from Mr. Hartley, who has charge of the work of maize investigation for the United States Department of Agriculture; he writes that they have experimented with various varieties of Indian corn obtained in Italy and the neighboring Balkan states, and that in all cases they were found to belong to the groups which they classify as *small yellow or orange colored flints*, and that they resemble in their physical appearance our *yellow pop corn*. Sturtevant classifies the *red* cuzco as belonging to the group of soft corns, and in this view he is sustained by Burtt-Davy in his well known monograph on this subject. The authority last quoted says that the *red cuzco* does not keep well on account of its softness, being readily attacked by weevils and other insects. It would then appear that the consistency of the grain has no relationship to the ease with which it may be attacked by moulds, since all authorities agree that this variety of maize practically never becomes infected with these parasitic organisms. It thus seems that there is some characteristic of certain varieties of Indian corn that conduces to their remaining sound, even for long periods of time, which is not at present understood, and the subject therefore becomes an inviting field for further investigation.

In addition to the relationship of what appears to be certain inherent properties of different varieties of maize to mouldiness, there are other characteristics that bear strongly on their capacity to resist invasion by these microorganisms; it is known for example that other things being equal the cereal is attacked by the hyphomycetes directly in proportion as it contains moisture, and therefore all those conditions that make for an increase in its watery content before or after storage favor mouldiness. Such considerations bring forward a question of the greatest interest and doubtless of the highest importance in connection with the breeds of maize at present mostly used as food in America.

It has long been thought by the author that it is not improbable that the evident great increase in pellagra within recent years in the southern portions of the United States is more than likely in a measure associated with a change in the varieties of maize cultivated. He feels perfectly certain that thirty or forty years ago the flint breeds of this cereal were almost exclusively grown by the farmers of Georgia and Alabama, while at the present time it would appear in the same localities that only the dent varieties are cultivated. In visiting the corn shows annually held at Atlanta, Georgia, the author has been struck with the fact that almost always the dent breeds of maize were placed on exhibition, and he particularly noted that practically without exception a greater or less number of grains on every ear showed undoubted evi-

dences of mouldiness. If his memory serves him right—and of this he has no doubt—the flint varieties of the cereal formerly grown rarely exhibited evidences of decay except at the free end of the ear, at which point not uncommonly a few small and immature grains would be found showing such alteration; when prepared for grinding these bad grains were not, however, as a rule mixed with the mature seeds attached to the body of the cob, as the small end of the ear was quite universally cut off and discarded—this process being called "nubbing." It is particularly noteworthy that the mouldy grains of the varieties of maize which we now cultivate are by no means confined to the free end of the ear, but are everywhere intermingled with the sound grain, and as a consequence "nubbing" would by no means entirely free the shelled corn from a considerable proportion of bad grains. Thus we find that while it must be admitted that the varieties that are now commonly cultivated produce much larger and finer ears than those grown in the past, there can be no doubt whatever that the proportion of normal seed is much smaller than was formerly the case, and that any food products coming from the grain must therefore be less wholesome than in years gone by.

The author would have hesitated somewhat to put forward a view largely based on his own individual memory were it not for the fact that his testimony in this particular is borne out by that of others.

That the present varieties of grain cultivated by us are by no means ideal in every particular is asserted by Prof. Vanatter, who has charge of the maize investigation carried on by the State of Georgia at its experimental farms near Athens. The author exceedingly regrets that it does not appear advisable to introduce at this point a full and complete exposition of the views of Prof. Vanatter on this subject, but all of those who may be interested are referred to the appendix, where they will find the matter fully discussed in a very able paper that was expressly prepared for this volume (see appendix, p. 368). At this point it can only be said that Prof. Vanatter has shown clearly that the germination test proves beyond doubt that the breeds of maize cultivated by us are evidently defective. This is brought about in his opinion by a process of breeding that has caused a too sudden and, so to speak, a too violent variation from many of the chief characteristics of what he considers the parent plant, and which has resulted in marked deterioration. He particularly condemns the striving for enormous ears, which he believes results in many of the grains being immature, and a consequent tendency to subsequent decay.

In addition to the foregoing it may be observed that it is clearly established that certain varieties of maize are suited to certain climates, and it is not impossible that such factors have played a part in the evident deterioration which maize has recently undergone, at least in the southern parts of this country.

The conclusions of Prof. Vanatter are strongly sustained by entirely independent results of investigations in Italy. Thus we find that Frosini, who is one of the best Italian workers on this subject, has recognized the inferior quality of the varieties of maize commonly grown in this country, and he takes very strong ground against their importation and cultivation in Italy. He says:

"Indeed there has been substituted for our old types American varieties of maize, which, if more productive, are of inferior quality, and being of more tardy growth, and requiring more exact conditions for development, do not always mature" (p. 38).

The same writer mentions that the American varieties of maize contain a considerably greater proportion of *starchy endosperm* than do those breeds formerly grown in Italy, and as a consequence, as demonstrated by actual tests, the former absorb more water than the latter and are more prone to decay. This investigator has particularly condemned the breed known as *cento giorni* as being very hygroscopic, but gives no figures respecting the *cinquantino* and *quarantino*, which have been generally assumed by Italian writers to be most at fault.

It is not, however, probable that even if our knowledge respecting these different breeds of maize were more accurate, that the data would necessarily give us material aid in determining the least harmful of the different breeds of maize in this country, since it is well established that soil and climate play a most important part in the matter. Thus it is true, as just sated, that the *cinquantino* is generally considered by Italian investigators as the most likely of all the

different breeds of maize to become mouldy, but it is said by Neusser that this is far from being the case in Roumania, where the summers are dry and hot, and as a consequence the grain develops to great perfection. Most unfortunately there appears to have been little or nothing done in America in the way of determining what varieties of maize are best suited to our different climates—our whole attention having been directed toward procuring a heavy yield. As there can be no reasonable doubt whatever that pellagra is produced by bad maize, this subject most assuredly deserves our earnest attention, and offers a field for future investigation that bids fair to be of the first importance to our people. Quite irrespective of whether or not it should be ultimately determined that bad maize causes pellagra, the economic aspects of the question are of sufficient importance to cause those interested to use every effort to improve the breeds of maize commonly cultivated, as there can be no doubt that great waste necessarily results where breeds of maize are cultivated that easily undergo decomposition. As it is clear that it is out of the question altogether to abandon the use of this cereal, the most stringent regulations should be enacted both by the national and state governments with the view of limiting commerce in decomposing maize, and as far as possible preventing its use, particularly when mouldy. The seriousness of the problem has been fortunately realized by foreign governments, and there will be found in the appendix a translation of both the Austrian and Italian laws on this subject. (See appendix, pp. 376 and 377).

At this point attention may be called to an exceedingly interesting suggestion that was made by Gosio (9) some years ago; in view of the well-known fact that many of the lower forms of life show an extraordinary susceptibility to the presence even of the most minute traces of certain chemical substances, this eminent observer suggests that it might be possible to determine by proper investigation some agent that would prevent the development and growth of the moulds in maize, either by adding it directly after the cereal has been harvested, or possibly even placed in the soil with the seed at the time of planting; the suggestion is certainly worthy of further investigation.

(2) *Conservation.*—In some parts of the world, as in Mexico, the government builds granaries for the public, in which maize is kept and properly protected. While it is not probable that measures of this kind would meet with general approval in the United States, it would appear that our government could do nothing better than engage in an earnest campaign of education as to the proper construction of the cribs in which maize and other cereals are conserved. Nothing is more common than to see grain stored in leaky buildings, improperly ventilated, and in which rats, mice and other vermin live,—all of which might be easily avoided by a little intelligent care.

Gosio (9) particularly calls attention to the urgent necessity of taking proper care of *maize meal,* as he asserts that it offers much greater opportunities for the development of moulds than does the corn itself. He also agrees with Bonservisi when this observer criticises the lack of intelligent care in looking after the receptacles in which housekeepers preserve meal. In the great majority of instances vessels thus employed are not cleaned out from one year to the other, constantly therefore retaining more or less meal in a high state of decomposition, mixed with countless myriads of moulds and other microorganisms. Owing to the lack of all reasonable care, and the inherent tendency of meal quickly to become mouldy, Gosio asserts that *old meal is practically always synonymous with bad meal.* Antonini (7) has recently urged the use in the home of small hand mills, as being the best way of insuring a fresh supply of meal.

In view of the fact first demonstrated by Selmi that alkalies destroy the poisons produced in bad maize, it is interesting to note that in parts of Roumania maize meal is kept in bags covered by cow manure, which, while not particularly appealing to the aesthetic sense, may after all rest on a sound basis, for it is well known that ammoniacal vapors are abundantly elaborated in decomposing fecal material.

In this connection it is of great interest to note that Lapicque and Legendre have recently shown that the war bread now used in France is much improved by the addition of ammonia, and the former has still more recently suggested that lime-water would subserve the same end; LeRoy has still later asserted

that gluecosate of calcium—made by simply keeping ordinary quick-lime in a solution of sugar—is even better for this purpose.

(3) *Drying ovens.*—As it is well established that the ease with which maize ferments is directly proportionate to the amount of water that it contains, it was long ago proposed that the grain be protected by systematic drying in ovens. This process, which was first undertaken purely for economic reasons, appears to have originated in Bourgogne, in southern France, and was practiced for a long time before it was recognized that dessication was a measure of importance from a hygienic standpoint. That thorough drying of this cereal might influence its wholesomeness appears to have been first recognized by the great French pellagrologist Roussel (2), who strongly advocated the process for the purpose of preventing pellagra even so early as 1845. At a later time desiccation was introduced into Italy, first by Count Vicardo di Colloredo, in Feletis, in 1854, and, independently, by Antonio Reschisi, who established ovens for this purpose in 1860, at Corte Pelasio. Gradually it was recognized that the drying of maize is an important factor in the wholesomeness of the cereal, and as a consequence the government took up the matter and established ovens in various places in northern Italy; it is, however, said that the process of desiccation has not been carried out in that country to the extent that is desirable, and this neglect is doubtless more or less expressed by the continuance of pellagra as the national scourge up to a comparatively short time ago.

While the expense is slight the various difficulties in the way of properly drying the grain have, it appears, seriously interfered with desiccation being carried out to any considerable extent, and it seems doubtful if this could ever be done in America without the most stringent government regulations. Not only are the physical difficulties of carrying this out considerable, but in addition the procedure is almost useless without the grain is afterwards properly stored and properly cared for. As already noted, maize is decidedly hygroscopic, and if placed in damp or ill-ventilated houses would in a short time reabsorb sufficient water to permit repid decomposition. Romani has recently written an important paper of this phase of the pellagra problem in which he insists that drying maize is of but little value if the grain is not kept where it can so remain. He says in order that it may be kept free of moulds it should not contain more than 9-10% of water; in one lot of the cereal where it contained 18.72% of water practically every grain was mouldy. It is also said by Gosio that the drying should be carried out at comparatively low temperatures, and that sufficient heat should never be employed to kill the germ in the seed. The same authority likewise insists that a prolonged drying is much more satisfactory from every standpoint than a rapid carrying out of the process, there being under such circumstances less probability of the grain being devitalized, and likewise a less tendency later to reabsorb water. Drawings showing the methods of construction of the drying ovens commonly employed in Italy will be found in the appendix. It should be distinctly remembered that in using these ovens there could be no question of killing the moulds or many of the other organisms that are associated with decomposing maize, since it requires relatively high temperatures to accomplish this; our sole aim should therefore be merely to make the grain an unfit culture medium by removing its moisture.

(4) *Relationship of maturity of grain to mouldiness.*—The very earliest writers on pellagra—even before it was suspected that the cereal had any connection with the production of the disease—insisted on the unwholesomeness of maize that was not allowed to ripen properly. Generally speaking the harvesting of unripe grain in Europe has usually if not always been due to their short summer season, resulting in the plant being killed by frost before maturity. In Italy the growth of the plant is said to be quite often retarded by burrowing larvae—principally the *Agriotes*—injuring its roots, and thus causing the grain to ripen late and to be imperfect; an excellent article has been recently written on this subject by Caratti and Panizzi. Happily this difficulty has not been one with which we have had to contend in those portions of the United States where maize is grown, but unfortunately a practice has gradually developed in the western portions of this country that accomplishes the same undesirable end by artificial means. For something like fifty years in the region referred to it has

been the practice to cut the corn stalks before full maturity, and to shock them in the fields. Under such circumstances we have added to the bad effects of exposure to the inclemency of the weather the natural deterioration produced in the grain by it being harvested prematurely. After thus lying in the fields for months it is often gathered and shipped to distant parts of the country, and not uncommonly arrives at its destination in a condition so bad that it is even rejected as food for horses. This does not, however, prevent its being ground into meal for human consumption, and in this form no doubt becomes responsible for much of the ill effects that may be reasonably charged to this cereal. Quite irrespective of poisons that might be produced under such circumstances in the grain, it is certain that it loses much of its food value; the subject therefore becomes of economic as well as of hygienic importance. Most stringent laws against such practices should be enacted, and it is unquestionably the duty of Congress to see that maize so treated should not be permitted to enter interstate commerce.

(5) *Preparation of maize products for human consumption.—Mexican method.*—While it is known that pellagra occurs in Mexico, the disease would appear to be rare when it is considered that the starchy food of the great bulk of the population is made up almost or entirely of maize products. While it may be assumed that this is due to the cultivation of varieties of maize suited to the climate of that country, it has been suggested by Selmi, Neusser and others that the comparative immunity of the Mexican is the result of their method of preparing the grain for food. It is well-known that instead of grinding the grain, as is done in other parts of the world, it is there beaten up in a mortar after having been previously soaked in a strong alkaline solution until the husks may be readily removed. As was shown by the writers mentioned that alkalines destroy the poisons produced in maize by decomposition, it would seem entirely likely that after the treatment mentioned the grain would lose any bad properties that it might have acquired from fermentation, and would probably become wholesome. As it is, however, true that this grain appears naturally to contain substances that are mildly poisonous, it may be doubted if such treatment in reality renders it in every way a suitable food. The low order of intellectual development and the physical degeneracy which writers generally agree is so frequent among the common people of this unhappy country may now—as was thought to be the case at the time of the conquest—be due to the almost exclusive use of this cereal as a food.

(6) *Milling methods.*—That the method of grinding maize may more or less influence its wholesomeness is not improbable, and this result might conceivably be affected in two quite separate and distinct ways, namely,

(a) By degerminating the grain before being ground, and

(b) By removing vitamines with the husk.

(a) Inasmuch as all parts of the maize seed are covered by a thick and more or less impervious husk, with the exception of the small end of the grain in the immediate vicinity of the embryo, it has been assumed that the moulds principally penetrate at this point, and the majority of investigators have agreed that this is borne out by actual observation. If we accept the foregoing as true, it cannot be denied that the most common and most extensive seat of mouldiness must necessarily be in and around the embryo, and it therefore follows that any process of milling that gets rid of this part of the maize seed must of necessity be advantageous. This object is quite admirably accomplished by the more recent methods of grinding maize, there being brought about when they are employed a very satisfactory removal of the husk and a more or less complete degermination. As evidence that the newer processes are of value from a hygienic standpoint, we may instance the results of the investigation of Mariani, who operated with maize that was 50% mouldy; this was crushed in one of the more modern steel cylinder mills, and the various products were subjected to thorough investigation, with the result that it was found beyond question that the poisonous properties of the grain resided mainly in and around the embryo. These investigations were confirmed at a later time by Ghirardini (2), who likewise maintained that the principal seat of the pellagrous poisons is in the germ of the maize seed; this investigator also determined that the various

products obtained by the cylinder process of crushing show different degrees of toxicity, being most pronounced in the bran, or in that particular product that comes from the embryo. In this connection the researches of Colloidi should be referred to; this investigator was not able to discover that mouldiness ever occurs within the embryo itself, though he admits that the process is usually in the vicinity of this body. Contrary to the findings of Brizi, this author likewise asserts that he frequently found foci of mould infection within the endosperm at a considerable distance from and clearly having no connection with possible alterations in the neighborhood of the germinal portions of the seed; as to just how the organisms gain entrance he is uncertain, not having been able in many instances to demonstrate any break in the husk. This is a subject that would clearly repay a very thorough investigation.

It is of interest to observe that Colloidi has shown that the meal of the different varieties of maize presents no notable variations of resistance to mould infection, and it therefore appears clear that any immunity enjoyed by the different breeds of maize is entirely the result of the physical conformation of the grain.

(b) The theory that pellagra may be due to vitamine hunger has been recently advanced by Funk, but unfortunately, like most of the would-be givers of light in connection with this disease, he fails to furnish any experimental results upon which the view might be logically based. It seems not impossible, however, that the change in the method of milling within recent years in the South might afford a certain amount of confirmation of this view. A generation ago the eaters of maize products in the southern part of the United States were served almost exclusively by small mills using large stones to crush the cereal, and grinding up the grain in its entirety without the removal of the husks. Inasmuch as the vitamines are supposed to lie in the ordinary cereals just beneath the hard outer covering of the grain, it might seem not impossible that they are in a measure removed by the present methods employed, in which the grain is husked before being ground. However, the author does not for a moment believe that pellagra is a vitamine hunger, for the reason that all classes of society suffer from pellagra in the United States, and that even the poorest have sufficient variety in food to prevent such a contingency ever occurring.

It has been pointed out by Funk that in wheat the Folin-Macallum reaction may be obtained in a small zone just beneath the outer coverings, and he assumes that this is a consequence of the presence of vitamines. This reaction may also be obtained in maize, though the blue coloration in normal grains is well diffused throughout their substance. Particularly is this true of the smaller varieties of this cereal, that are called "prolific." It should also be noted that the blue coloration in the larger non-prolific varieties is much less intense, and not uncommonly the germinal portion of the grain assumes a greenish hue, which not unlikely is the result of the presence of phenols.

From the foregoing it becomes evident that if the blue coloration produced in this cereal by the Folin-Macallum reagents represents vitamines, the separation and discarding of the husks could have no effect on the vitamine content of the food product. Of interest in connection with the author's observation that pellagra has only appeared in the south since the non-prolific varieties of maize have been commonly grown and eaten, is the almost complete failure of this variety of the grain to give the Folin-Macallum reaction. Should this reaction really be a result of the presence of vitamines, and should it be determined that their absence is associated with pellagra, this failure on the part of the cereal to give the reaction is of much interest, and might be taken advantage of in testing maize products for their wholesomeness; this could easily and probably better be done by making an extract from the meal than by testing the whole grains.

Likewise the view that pellagra is a vitamine hunger seems negatived by the apparent infrequency of pellagra in Mexico, where, as already noted, the grain is boiled and husked before coming to the table: however, if we may assume that the Folin-Macallum reaction is a true test for vitamines, Funk's illustrations might explain the discrepancy, since they show that after cooking the depth to which the content of the maize seed reacts to the reagents employed in this test is greatly increased.

(7) *Alcoholic drinks prepared from maize, and pellagra.*—It was shown many years ago by Neusser (1) that there is not improbably a relationship between pellagra and the consumption of alcoholic drinks made from maize,—this investigator believing that the poisons that produce this disease are volatile and pass over with the alcohol during distillation. As to whether or not pellagra is produced in this way has not as yet been definitely determined, though the views of competent clinicians are rather against the probability of such a connection. It is, however, a matter that deserves attention, as there is no question but that an affection closely resembling pellagra is not uncommonly associated with alcoholism, and that whatever the condition may be, it could hardly be regarded as negligible. One of the effects of prohibition in the Southern States is that there is an enormous increase in the amount of "blind tiger" whiskey sold, and this is as a rule nothing more than the poorest kind of whiskey made from maize.

(8) *Substitution of other cereals for maize.*—All pellagrologists are in agreement as to the desirability of substituting potatoes or other cereals for maize, and it may be asserted that wherever this has been brought about that pellagra has gradually disappeared. No clearer example of this could be possible than the history of pellagra in France, in the southwestern part of which country it prevailed to a considerable extent about the middle of the last century. Owing to the teachings of Roussel, Costellat, Tardieu and others, maize was there gradually abandoned as a food for the human being, with the substitution of potatoes and other cereals, and as a consequence this malady has entirely disappeared from France.

On account of the ease with which the plant may be grown—developing well in poor soil and requiring little or no cultivation—Ferretti has advised that buckwheat be substituted for maize.

While it is not probable that it will ever be possible entirely to do away with maize in this country, the dangers of the use of the cereal should be generally taught, and the people urged to use it as little as possible, and then only when of the best quality. Unfortunately it will take at least a generation to bring about a cessation of the disease, even after every precaution possible has been taken.

(9) *Proper food and good hygiene as preventive measures.*—As has been recognized from the earliest days of the study of this disease, pellagra is an affection that is most commonly associated with bad food and unhygienic surroundings. It is preëminently a disease of the poor, and is very commonly associated with filth. All pathologic states that have a tendency to produce a chronic lowering of vitality act as predisposing causes to this malady, such affections as syphilis, malaria, and uncinariasis being very frequently associated with it. We should, however, never lose sight of the fact that hardships, bad food, and unhygienic conditions generally, even when associated with other chronic diseases, are unable alone to produce pellagra, and that this malady does not occur without the operation of its special causative agency. This should be impressed upon our minds particularly at the present moment, since there is a revival in the United States of the ancient and oft repeated idea that pellagra may be produced by inanition, and it is clear that this view will undoubtedly result indirectly in much damage without an earnest effort is made to acquaint the general public with the facts in the case.

From the time of Odoardi the idea has prevailed in Italy that absence of proper quantities of salt from the dietary is in a certain degree associated with the production of pellagra. So strong was this feeling that a section was incorporated in the Italian law of 1902 for the prevention of this disease, which made it mandatory on the Minister of the Interior to furnish salt to families whose members show a tendency to become pellagrous. More recently this connection has been insisted upon particularly by Randi and Deganello, and still later by Camurri (2, 8), the latter having shown that there is a gradual loss of all mineral salts from the body in this disease. It would thus seem that there is some scientific basis for this old popular idea, and it is therefore advisable for those who have developed pellagra, and for the members of their immediate families, to partake of abundant quantities of this substance. It should, however, be pointed out that in this country salt is very cheap, and that even the poorest

are adequately supplied with it, and that consequently its abundant use does not prevent the development of pellagra.

This terrible disease has proved such a scourge in Italy that the government has found it necessary to build and maintain a large number of institutions for the benefit of its victims. There are hospitals for the worst cases (pellagrosari), for those not so bad establishments where the patients are fed and given proper medical attention, while continuing their regular occupation (locande sanitorie), and still others where their grain is properly dried, their flour and meal made into good bread at the lowest possible cost, and their mouldy maize exchanged for good wheat (forni rurali); also, either alone or associated with some of the foregoing, there are operated plants for drying grain (essiccatori). In some provinces they have homes, something like our poorhouses, where aged, infirm and indigent pelligrins, no longer suffering from the acute phases of the malady, may be looked after (casa di recovero). These institutions are well described in the remarkable monograph on pellagra by G. Strambro (Jr.), the brochure by Gris, and papers by Manzini, Patrizi, and particularly Ceresoli (1).

For a discussion of the special precautions that should be taken by those who have once shown symptoms of pellagra the reader is referred to the chapter on treatment.

Detection of bad maize.—Inasmuch as any successful fight on pellagra is inextricably connected with diminishing the consumption of mouldy maize, the physical and chemical peculiarities of the grain under such circumstances becomes a matter of interest and even of great importance. It is therefore thought that no apology is necessary for the insertion at this point of some remarks on this subject, together with a description of the chemical methods employed for the purpose of determining the presence or absence of mouldiness.

Good maize presents a shining appearance and a slight characteristic odor, and a faintly sweetish taste. Should the grain exhibit a musty odor, even in the slightest degree, or should it have an acid-like smell, its soundness may be well doubted. Where mouldiness has taken place to any considerable extent the grains usually present a dark bluish appearance, while others retaining more or less of a normal hue are found to be soft and friable, and evidently undergoing decay; when properly matured and preserved carefully never more than 5% of the grains should show evidence of alteration. On being planted at least 80% of the seeds should germinate; in this connection it should be noted that where the cereal is dried at a high temperature, or even where this is done too rapidly at a lower degree of heat, the power of germination is frequently destroyed, even though the grain may be otherwise sound. On being burned there should not remain more than 4% of ash. Extracts of the cereal when injected into animals should not produce in ordinary quantities any appreciable symptoms, and the grain is to be regarded as being bad when this occurs.

The following methods are those that are employed for the detection of mouldy maize, and while none of them are alone ordinarily of such determining value as to permit the results obtained to be considered as decisive, a combination of two or more of them, giving corresponding results, are usually quite sufficient to justify a decision as to the wholesomeness of a given specimen of this cereal.

Sclavo's method.—Of all of the methods devised for the testing of maize, perhaps after all the most satisfactory is that of Sclavo, which depends simply on the germinating power of the maize seed. The method is, however, open to the objection that it takes several days to carry it out. Furthermore it is well known that the maize seeds may be and frequently are more or less mouldy at a sufficient distance from their embryos to interfere in no way with their power of development. The test is also somewhat misleading in that in some instances an unusually large percentage of grains fail to germinate, notwithstanding that the degree of alteration is slight, there being in reality not such a great proportion of decomposition as might occur in other cases where a fewer number of grains are attacked, but at the same time decayed throughout.

The test is carried out as follows:

A layer of moistened cotton is laid in the interior of a glass or porcelain vessel, and into it 100 of the maize seed, selected at random, are placed, with the small end mashed down into the cotton. The whole is covered and set aside

for two or three days at a temperature of from about 94° to 98° F., and at the expiration of this time the germinating grains are counted; at least 80% of the seed should germinate, and the maize could hardly be looked upon as being good without the percentage were 85% or 90%.

Instead of placing the maize seed in cotton Gosio recommends that a special apparatus be constructed, consisting of a glass vessel into which a diaphragm fits containing 100 holes of sufficient size to receive the seed. Water is placed in the bottom of the vessel and the diaphragm supported above it, and after the seed are properly arranged in the receptacles mentioned the apparatus is covered and the rest of the test carried out as previously directed.

A larg number of chemical tests have been suggested.

Among the first of these was that suggested by Lombroso and Dupré, who found that when maize is placed in 90% alcohol the latter assumes a reddish hue, which is dark in proportion to the alteration in the maize. The same investigators noted that maize soaked in a dilute solution of caustic potash changes the color of the latter to a reddish-brown tint if the corn be bad.

Alpago-Novello (3) has observed that when a mush is made by adding acetic acid to mouldy maize meal and allowing it to stand for 24 hours and filtering, the clear filtrate gives a violet colored precipitate when tannic acid and ammonia are added in excess.

Another test that has the advantage of being simple and convenient is noting the facility with which meal made from bad maize undergoes putrefaction; to carry out the test a little water is added to the meal, and the vessel containing the mixture is placed at a temperature of from 95° to 98° F., and in case considerable decomposition has previously occurred a fetid odor develops within about six hours and rapidly grows worse.

So great is the tendency of maize that is unduly moist to become mouldy that an excessive quantity of this fluid in the grain may be actually looked upon as a test of its soundness; it was long ago shown that moisture in excess of 14% is almost always sooner or later associated with decomposition, and when we find therefore that a maize has so great a proportion it should be looked upon with suspicion.

It has likewise been shown that the nitrogenous content of maize is decreased when decomposition sets in, which is also associated with a great diminuation in fats.

Tiboli has shown that the reducing power of bad maize is much above the normal.

Test for acidity.—Of all the chemical tests so far proposed for bad maize the one devised by Tiboli which depends on an increase of acidity during decomposition is unquestionably that which has been found to be of most universal application; unfortunately, however, this test is not entirely to be relied upon, for the reason that the increased acidity produced by decomposition of the starches into acids not uncommonly decrease as basic substances are later produced by putrefaction in the albuminous constituents of the seed,—the latter process sometimes going on to such an extent that a very acid maize may ultimately become actually alkaline. This test is therefore only of value where an ordinary degree of change has occurred, and would not give satisfactory results where decomposition had been going on for a long time, or was of a very marked character.

The test is carried out as follows:

10 grams of ground maize meal are added to 60 c. c. of 80% alcohol. The mixture is placed in a stoppered bottle and laid aside for some hours, with frequent agitations; 30 c. c. of the liquid are then decanted and mixed with an equal quantity of water, after which a few drops of phenolphthalein solution are added, and the acidity determined by titration with decinormal sodium hydoxide solution; the acidity should not be greater in 100 grams of meal than the amount necessary to neutralize 25 or 30 c. c. of the soda solution.

Gosio's phenol reaction.—A number of years ago a reaction was described by Gosio for testing decomposition in maize, but its results appear to be of somewhat doubtful value, since there has been considerable contradiction, even in

Italy, as to the reliability of the method. Some, like Ceni (19) and Ceni and Besta (4), have maintained that the test is uncertain and of no value, while on the other hand Paladino (3), Ori, Lui (2), Ghirardini (1) and others speak well of it. Unfortunately, as shown by Alsberg and Black, the moulds affecting maize in America do not appear to produce the substances that give this reaction, and the test would therefore appear to be of but little interest to American pellagrologists; however it is possible further investigation may show that the moulds giving rise to it may occur in maize in some parts of the United States. It is not, therefore, thought wise to omit the procedure. The test is made as follows:

50 grams of maize meal are mixed with 150 c. c. of 90% alcohol, and the whole boiled for about two hours; the mixture is then filtered through linen, the material in the bag finally squeezed, and after settling a short time the filtrate is again filtered through filter paper; the second filtrate is then placed on a water bath and evaporated down to about 7 or 8 c. c. Lui recommends, on account of the dark nature of the liquid mass that remains after evaporation, that the latter be evaporated almost to dryness and then taken up with a few c. c. of boiling water, and then the whole filtered while hot, after which the test may be made. Gosio recommends that after the alcohol filtrate has been evaporated down as just directed that it be divided and placed in two separate capsules and allowed to cool, and without delay a 1% solution of ferric chloride is added to one of them drop by drop with continued agitation; inasmuch as a slight excess of the ferric chloride tends to destroy the blue or greenish color produced when the reaction is positive, by taking note of the number of drops of ferric chloride that produce the greatest degree of color in the capsule first used the precise amount of this reagent necessary to give the deepest tone can then be added to the second capsule, which may be kept for purposes of comparison if so desired. Inasmuch as all of the maize products of commerce in Italy give this reaction to a certain extent a considerable amount of practice is required in order to interpret the results intelligently.

Gosio remarks that the phenol substance that gives rise to this reaction may be obtained in comparative purity by treating the aqueous residuum that remains after evaporation with ether; the latter may then be evaporated, the residue taken up with water, and the test made.

Following the principles referred to in the chapter on the mould toxines Di Pietro (3) modified the test of Gosio as follows,—the procedure being based upon the observation that the ferric chloride reaction is very greatly strengthened if the culture be previously acidified, and particularly if it be still later boiled.

A sufficient quantity of material (about three ounces) is boiled for a minute with a 2% aqueous solution of caustic potash, after which it is acidified with sulphuric acid and again boiled for a few seconds; the mixture is then agitated with an equal volume of petroleum or benzine and the latter decanted and treated in a test tube with 2 or 3 c. c. of a mixture of 1 part of alcohol, 3 of hydrochloric acid, and 1 of ferric chloride; the mixture is agitated, after which in a little time the reaction occurs in the bottom of the test tube, the color being almost black where the quantity of aromatic substance is considerable. The reason that the potash solution is used is that it has been determined that the phenol compounds when forming salts with caustic alkalies are much more soluble than in their primitive condition.

This author asserts that this test is never given by sound maize, and only occurs where the cereal has been acted upon by moulds.

Where the quantity of phenol compounds is so small that the test is not given in this way, recourse may be had to cultivation. In this case a few centigrams of the suspected material is suspended in a couple of c. c. of sterilized water, the mixture placed in several test tubes, and to each is added a small amount of sound maize which has been previously sterilized in a 0.5% solution of hydrochloric acid; the test tubes are then kept at ordinary room temperature for about five days, after which the test for the aromatic substance is made as heretofore indicated. Acid glucose agar may be used in place of the maize medium for growing the moulds if so desired.

Ori's peroxide of hydrogen test.—Some years ago Ori devised a test for bad meal which depends upon the fact first shown by Giusti that enzymes produced

by moulds possess the property of causing decomposition of hydrogen peroxide. The method appears to be delicate, but unfortunately it seems that maize, particularly after the changes are initiated that occur in connection with the development of the embryo, possess enzymes that decompose this substance quite as readily as do those that are formed by moulds. For this reason Lui (2) maintains that the test is worthless, and Ghirardini (1) has more recently sustained this view to all intents and purposes. It is said by Gosio (9) that most meals give rise to this reaction, and that it is a matter of much difficulty to interpret properly its results. The test is carried out as follows:

5 grams of maize meal are extracted with 15 c. c. of a 50% solution of glycerine in water; after being well shaken it is allowed to settle for half an hour, after which it is filtered; 1 c. c. of the filtrate is then placed in a test tube of small diameter and to this are added 4 or 5 drops of Merck's hydrogen dioxide which has been previously diluted 10 times with water; the evolution of gas is construed as indicating a positive reaction.

The cumarine test.—As is well-known, Gosio (6) a number of years ago demonstrated the fact that cumarine is produced as the result of the life activities of mouls when grown in contact with starches; the detection, therefore, of this substance in starchy food-products is certain evidence of the development in them of the hyphomycetes. It should be remembered that cumarine is not thought to be the real pellagrous poison. The test for this substance is carried out as follows:

5 grams of meal are placed in an extraction apparatus, acidified with a few drops of a mixture of sulphuric acid 1 part and water 3 parts, and to the mixture there are then added 20 c. c. of ether, and the whole is repeatedly agitated for half an hour; the ether is then decanted, washed with distilled water, and evaporated down until only a small moist mass remains, and there are then added a few drops of an aqueous 10% solution of caustic potash; a positive reaction is shown by the development of a beautiful rose or violent tint, which is accompanied by the production of the odor of perfume. In case of a negative result the residuum may serve for the perchloride of iron test by simply rendering it acid and making a new extraction with ether.

Physiologic test.—It has long been known that extracts from mouldy maize are decidedly toxic, and that they will produce marked symptoms and even death in animals if injected in sufficient quantity. Some years ago Gosio and Paladino suggested taking advantage of this fact in testing the quality of maize products, and carried out the experiment in the following manner:

For this purpose they make an extract with 90% alcohol, just as when preparing for the phenol reaction, and, after evaporating, redissolve the residue in water and use it for the purpose of injecting animals employed for the test. The quantity of the extract that should be used depends on the size of the animal; if a guinea pig or a young rabbit is employed the entire amount of the extract about from 50 gm. of maize meal may be given, but where rats or mice are used about one-fifth of this quantity is sufficient. The inoculation should be made beneath the skin, and the parts afterwards rubbed in order to cause a rapid dissemination of the poison. A positive result is shown by spasmodic contractions and paralysis of the leg muscles coming on in from 10 to 15 minutes, which symptoms usually gradually increase until the maximum intensity is reached after about three-fourths of an hour following the injection. In some cases the animal dies, but rather more commonly recovery occurs.

In concluding this discussion the author would remark that it is agreed by the best authorities that much practice and a great deal of judgment is necessary in coming to a decision as to whether or not maize is fit for human consumption. It is unfortunately true that all maize is more or less mouldy, and that as soon as the process begins there are produced immediately the several physical and chemical alterations upon which we depend for determining as to whether or not it is wholesome, and it is therefore a rather delicate matter, if we are to eat this cereal at all, to determine at what point the boundary is overstepped between the good and the bad. This should not, however, deter us from giving this subject our most earnest attention, and we should remember that not only is this a matter that affects the physical well-being of ourselves and of

generations yet to come, but that the problem is one which is also of great economic importance.

Isasmuch as it appears that mouldiness of maize is not produced by the same organisms in America as in Europe, a study of this subject becomes for us a matter of the highest importance, and it is to be hoped that someone will earnestly take up the matter, already begun by Alsberg and Black, and repeat here studies similar to those carried out by Gosio in Italy with so much ability and such brilliant results.

Sanarelli (1) has recently advocated the passage of laws in Italy which would prevent absolutely the milling of bad maize. That great progress was, however, being made under existing laws was shown by the same writer (2). In the census of 1899 it was shown there were in the kingdom 72,603 pellagrins, while in 1905 the number had decreased to 55,500, the law against the use of bad maize having gone into effect in 1902. In the three years from 1900-1902, inclusive, 9,218 people died in Italy from pellagra, while from 1903-1905, inclusive, 7,367 died, and in the three years from 1906 to 1908 inclusive, the disease carried off only 4,649! As further evidence of the effectiveness of the law in the year 1907 there were 4,950 new cases of pellagra in Italy, while in the succeeding year there were only 2,824 fresh cases. Unfortunately these results are of not such significance as would be the case if we were dealing with almost any othr disease. Better economic conditions, with more and better food could easily account for the improvement, as it has been clearly shown that under such circumstances pellagra becomes less common and less severe,—the disease simply lying dormant. A much greater length of time is necessary really to get rid of this terrible malady.

CHAPTER VIII

TREATMENT.

With all of the progress that has been made in our knowledge of the causation and pathologic alterations of pellagra, no corresponding advances in its treatment has followed. This, however, is far from being the result of indifference on the part of pellagrologists, for the tremendous literature on this disease bears abundant evidence of their interest in this phase of the subject, and of their constant attempts at improvement in the therapy of the disease. To one, however, who has given attention to the works of those engaged in the study of the pathological histology of this affection this state of affairs presents nothing whatever of a surprising nature, for such a one could only regard a complete cure as being the result of a miracle. When we contemplate the profound alterations throughout the nervous system, consisting of the destruction of nerve cells and their processes and their replacement by scar tissue, the widespread alterations in the walls of the smaller blood vessels, the low grade of so-called inflammation accompanied by productive processes in the various viscera, with disturbance of their functionating capacity, the atrophy of the muscular tissues, and softening of the bones, the profound changes in the skin, and in the mucous membranes of the mouth, throat, esophagus, stomach and intestines, and when we recall that a large proportion of these lesions in their very nature could never be entirely removed, the difficulty is not in understanding why we have found no drug that acts as a specific, but rather are we astonished that so many patients temporarily recover from the acute attacks, and frequently continue to live in fairly good condition for many years after the external symptoms have made their appearance.

At this point especial attention should be directed to a fallacy so common, and one to which so many otherwise competent medical men have subscribed, that the error has almost become respectable; this is the widespread belief that the adventitious, and, one might say, almost accidental external symptoms encountered in pellagra in reality constitute the disease itself, and that when such manifestations are relieved that the patient may be regarded as being cured. Unfortunately, however, nothing could be farther from the truth or more to be deplored, for not only has this mistake resulted in much

self-deception among medical men, but it forms the basis of an appalling amount of fraud; based on this fundamental error the pathetic victims of this disease fall a ready prey to the unscrupulous quack who at present fills the advertising columns of the newspapers in the southern parts of the United States with unqualified promises to cure this incurable disease, and adds to the misery these unfortunates have to endure by taking from them the little money that they may possess. It is high time that our national government should take cognizance of this matter, and see to it that the trickery and decepion should no longer flourish at the expense of the diseased and ignorant.

In the treatment of pellagra there are two quite separate and distinct problems which should be clearly disassociated from each other; the first and more pressing of these is that of relieving the sufferers from this disease, as far as lies in our power, of the external and more obvious symptoms which together constitute what is ordinarily called an attack of pellagra; the second is to aid as far as possible the victims of the malady in the intervals between the attacks, and to do everything possible in the way of preventing the frequent recurrence of the more pronounced manifestations.

Before proceeding further it should be insisted that *good feeding forms the basis of all treatment in pellagra,* in whatever stage the patient may be encountered. In Italy, where this disease has existed nearly two hundred years, and where it has been studied as nowhere else, and likewise in Austria and Roumania, the universal consensus of opinion among competent pellagrologists is that good feeding is the sheet anchor in its therapy. Even in the earlier days of the study of pellagra, at a time when it was the universal ambition of medical men to discover specifics and to treat the disease rather than the patient, it was generally agreed by students of this affection that nothing was so efficacious as proper nourishment. Thus we find that Casal relied mainly on *good food* and *milk products,* and that Strambio, the prince of pellagrologists, insisted that *animal food* was a *sine qua non* in the management of this disease. The great advantages of *milk* in the treatment of the malady was first clearly recognized by Soler, who looked upon it as being in the nature of a specific. As evidence of the sanity and admirable power of observation of the earlier pellagrologists it is interesting to observe that almost without exception they recognized the great importance of good feeding; thus we find that Odoardi recommended the *flesh of young animals,* Albera *fresh meat, eggs* and *milk,* Della Bona *milk* from the *breast,* Gherardini *meat* and *abundant food,* Allioni an *adjustive died,* Facheris *good meat* and *wine,* Parmentier and Deyeux *milk,* Fanzago *milk* and *good food,* Holland *good food,* Nardi (2) a *generous diet,* Marchand *milk,* Cales a *substantial nourishment,* Ballardini (1) *animal food,* Robolotti *good nourishing food,* Roussel (2, 3) *animal food,* Morelli *nitrogenous food,* and Lussana and Frua *nitrogenous food.* Likewise we find that the directors of the pellagra hospitals, and the foremost Italian, Austrian and Roumanian clinicians of the present time place the greatest reliance on the character of the food given

the patients. Thus *meat, milk* and *good wine* are recommended by Bennati, and a generous diet by the lamented Fritz (1), late chief of the medical staff of the pellagra hospital at Inzago; we could do no better than to quote from one of the papers of this careful observer, which was written some years ago. He says:

"From Casal down to the more recent of our illustrious experts on pellagra the view has prevailed that a proper regimen and good hygiene are the best remedies for this disease; that not in medicines but in good hygiene and proper dietetics are to be found the principal means for both treating and preventing pellagra. The microscope may indeed contribute to raising the study of this malady to the dignity of a science, and it may enrich its bibliography and advance our theories, but the hygienico-prophylactic treatment has received thorough confirmation, and has been demonstrated to be of real value. It is of course necessary and indispensable that students should continue their indefatigable labors to discover the precise agent that produces pellagra, but we in the field of curative medicine have properly pursued a more rapid method. For myself, after many years of practice, observation and comparative studies, I admit the poisonous properties of maize when bad, or when it is formed into bread in a state of mouldiness and fermentation * * *. The lead treatment I must frankly say is of no value in this disease; not that I would utterly discard drugs in the treatment of concrete symptoms, or as aids in connection with the treatment by good food and hygiene."

Let us not assume, however, that this great pellagrologist was for a moment deceived as to the possibility of curing pellagra, in the real sense of the word, for he is the author of the aphorism "Pellagra may be prevented, but not cured."

Quite agreeing with the authority just quoted, we find that Bennati, of the pellagra hospita of Ferrara, says that at this institution the treatment is *principally dietetic,* the patients being given a *highly nitrogenous diet* consisting of plentiful quantities of milk, meat and good wine. Likewise Fabbri, of the pellagra hospital of Umbria, agrees that a careful diet *consisting largely of meat* is essential in the treatment of pellagrins.

Entirely in sympathy with the foregoing are the great Italian clinicians Majocchi (2), Devoto (3), and Agostini (6), all of whom particularly insist that the *dietetic treatment* is the one that is of most avail in this disease. The Austrian pellagrologist Berger is also of the same opinion, as is Pearson, who has had much experience in the treatment of pellagrins in Egypt.

In this country the author has from the first insisted on the preëminent part that good feeding plays in the therapy of pellagra, and has urged it in the various bulletins on this subject written for the Georgia State Board of Health, and in his article on this disease in Hare's "Modern Treatment," which was published in 1911.

From the foregoing it is clear that all are in agreement as to the superlative value of good food in the treatment of pellagra, and

that this view is by no means a recent discovery, as certain articles recently published in the United States would lead us to believe.

The author then would recommend as the *sheet anchor in the treatment of pellagra the administration of good food, combined with rest in bed, out of doors if possible, and good nursing.*

During the acute pellagrous attacks nothing has appeared to be of so much value as milk, given in as great quantities as the patient can bear. Where the stomach is much upset it is frequently necessary to administer the milk in small quantities, though when this is the case the intervals between feeding should be short. In some cases the milk is taken better when boiled. Where the patient rebels against a proper quantity of milk matters may be often materially helped by evaporating it down to about half of its original amount, and giving this in whatever quantities can be taken. In some instances the addition of alkalies is likewise of value; a tablespoonful of lime water, or five grains of bicarbonate of soda to each glass of milk will often prevent nausea, and should be resorted to whenever this aliment seems to disagree. It is a matter of the greatest importance to make the patient take the milk slowly, as otherwise large curds are formed in the stomach where its secretion is not entirely suppressed, and its digestion therefore made difficult. If the mouth is not too sore the taking of the milk with bottle and nipple is the most satisfactory way of giving it, but where the condition of the oral cavity prevents the patients may be fed very slowly with a spoon.

In the place of milk raw eggs may be given, or, where the whole egg disagrees, only the whites; in some cases the raw eggs agree when the milk does not. It is frequently very satisfactory to administer the milk and eggs together, the latter being shaken up with the former in the form of a milkshake, to which a little sugar and flavoring may be added if the patient so desires.

Volpi many years ago recommended that the blood of slaughter houses be collected, and given to pellagrins either raw, or prepared in a suitable manner.

As the acute symptoms begin to subside cooked eggs may be allowed, and at the same time broths may be added, and still later purées and other soups; as the patient's improvement continues fish, if it can be procured fresh, and still later well-cooked and tender poultry or game should be given, to be followed finally by a resumption of the ordinary diet. Notwithstanding the fact that bad maize is recognized by practically all Italian, French, Roumanian and Austrian authorities as the cause of pellagra, on account of its cheapness this cereal is frequently given in small quantities to patients in the hospitals after improvement begins, though particular care is taken to secure meal from perfectly sound grain. In this connection it is interesting to observe that some years ago Tibaldi and Alpago-Novello found that 40 per cent. of their cases of pellagra improved at once when the bad maize upon which they had been living was withdrawn, and they were fed upon the unfermented products of this cereal.

As an example of the kind of diet allowed in the pellagra hospitals of Italy the following dietary taken from a recent paper by the distinguished pellagrologist Agostini (6) is not without interest:

Sunday. Dry bread, 6½ ounces; meat stew, 4½ ounces; rice and bacon, 3½ ounces; vegetables.

Monday. Rice and vegetables, 3½ ounces; omelet made of two eggs; lentils with oil, 5 ounces; salad, 0.67 ounces.

Tuesday. Corn mush and bacon, 6½ ounces; veal stew, garnished, 4 ounces; bread and bacon, 4 ounces; vegetables.

Wednesday. Beans and bacon and bread, 5 ounces; 2 eggs; bread and bacon, 4 ounces; salad, 0.67 ounces.

Thursday. Bread and broth, 4 ounces; roast beef, garnished, 4½ ounces; rice and bacon, 3½ ounces; vegetables.

Friday. Beans and bacon and bread, 5 ounces; cod fish stew, 3½ ounces; bread and bacon, 4 ounces; vegetable omelet.

Saturday. Corn mush and bacon, 6½ ounces; omelet of 2 eggs; lentils with oil, 5 ounces; cheese, 1.67 ounces.

Every individual has daily 22 ounces of bread, and 1½ ounces of wine.

Where pellagrous patients are too ill to take proper quantities of food acidosis is a frequent and very fatal complication; we should therefore endeavor to prevent this by seeing to it that as much carbohydrates as is possible be taken in such cases, and that alkalies be added wherever this complication appears imminent.

In the intervals between the attacks the patient should lead a very careful and well-regulated life, and all excesses should be avoided. He should sleep as much as possible, should never overwork, and should avoid manual labor involving exposure to the sun,—particularly in the spring of the year; at this period he should likewise live on simple and highly nourishing food. For years it has been the practice of the author to advise his pellagrous patients to go to bed, and live on milk and raw eggs for at least a month in the spring of the year,—the treatment to begin two or three weeks before the period corresponding to the onset of the previous season. At such times also a change of climate, particularly where there is a marked difference in altitude, is often of great advantage; therefore patients living in the mountains should go to the seashore, and vice versâ.

Where pellagrins are poorly nourished Antonini (9) has proposed a measure which is doubtless destined to prove of great value, this being the injection of pure, sterilized olive oil into the subcutaneous tissues of the thigh; he begins with 50 cc. (1 2-3 ozs.) and increases to 150 c.c. (5 ozs.) of the oil daily for about two weeks. Doubtless cotton seed oil would answer quite well. Care should be taken that the oil is not introduced into a blood vessel.

Injections of extracts of mouldy maize.—While there can be no doubt that rest, good and assimilable food, and change of climate are of the utmost importance both in preventing recurrences of the acute pellagrous attacks, and in warding off the graver symptoms in patients who have only suffered from the milder forms of the disease, and

while such measures will in all probability continue to be our sheet-anchor in the treatment of such cases, this discussion would not be complete without calling attention to certain results which have been recently obtained in the prevention of the classical pellagrous onsets by means of injections of extracts of bad maize.

As has been aready pointed out, it was long ago discovered by Devoto, and his assistant Ascoli, that pellagrins exhibit a hypersensibility to extracts of bad maize, and that the conclusions of these writers were fully confirmed by the later investigations of Volpino, Mariana, Bordoni, Alpago-Novello, Cesa-Bianchi, Rondoni, and others. Somewhat later it occurred to Volpino that a state of resistance might be established by repeated injections of such extracts, and he, in conjunction with Bordoni (1, 2), reported the results of his earlier investigations in the latter part of the year 1913. These observers began their work by repeatedly injecting rabbits intravenously with extracts of bad maize. Ten days after discontinuing this treatment some of the blood serum of these animals was mixed with solutions of what they have called "pellagrogenina" of varying strengths, and the mixture administered subcutaneously to guinea pigs that had been sensitized to maize products by feeding them on these substances, and it was found that the animals suffered no evil effects as a result of the injections, and it was, therefore, felt that antitoxic bodies were evidently contained in the serum used.

Following the foregoing experiments these investigators treated three patients in the fall of 1913 with injections of gradually increasing strengths of extracts of bad maize with what appeared to be excellent results, and they have just reported a continuation of the work along these lines which was done in 1914, and make mention of the fact that the well-known pellagrologist Camurri has informed them by letter that he has also seen striking effects from the treatment.

Still more recently Finato and F. Novello have reported the results of the use of the extract in fourteen cases, and have expressed themselves as having a high opinion of the efficacy of the treatment in many cases: in only one of the fourteen persons treated was there even any doubt as to the beneficial effects secured.

Inasmuch as it takes some little time to carry out this plan of treatment, it is considered best for the patients to take it during the fall or winter.

In some instances the medicament has consisted only of concentrated solutions of extracts of bad maize, and, what seems better, in other cases "pellagrogenina" has been employed. Whatever extract of bad maize is used, the utmost care should be exerted in seeing that the solution is properly sterile; in some cases the investigators in testing for hypersensibility have sterilized the solutions by heat, but on the whole it would appear to be much better to filter the extracts through a Berkefeld or Chamberlin germ-proof filter, as only in this way would it be possible to preserve all of the component parts of the bad maize intact.

Gradually increasing strengths of the solutions are employed, the patient being carefully watched in order to avoid the occurrence

of pronounced reactions, which, in case the solutions used are too strong, much resemble those obtained by tuberculin in patients with tuberculosis.

Ordinarily the injections are given every other day, and it requires about two months to complete the treatment, this being continued in gradually increasing doses until reactions no longer occur, even after the use of very strong solutions.

The results obtained by the well-known pellagrologists whose names have been already mentioned are such as to warrant a thorough investigation of this method of treatment. While it is certainly impossible ever to remove the extensive pathologic alterations that are always present in pellagrins, there is no question that we may by proper measures ward off the acuter manifestations in many instances, and should it be found that this treatment is of any decided value for this purpose it would certainly be a God-send to the unfortunate victims of this disease.

Baths.—From the time of Frapolli baths have been recommended in the treatment of pellagra, the authority just mentioned having particularly recommended them. They have been also thought to be of value by Strambio, Roussel (2, 3), Ercolano, DeOrchi, and many others. The feeling of Italian pellagrologists on this subject may be summed up in the following resolution which was unanimously agreed upon by those attending the first Italian pellagra conference in 1899:

"That the Congress holds for combatting pellagra, outside of good food, medical treatment is of use in some cases, and of these arsenical therapy and the treatment by baths appear to have given the best results" (Transactions First Italian Pellagra Congress, p. 154).

By some it has been thought that sulphur baths are particularly beneficial, while others have recommended sea baths. It seems to have been generally agreed that these baths should not be too cold, the temperature usually recommended being somewhere near that of a human body. Ercolano, who has given this matter particular attention, advises that the temperature should be about 82.2° F. (25° Reaumur).

Internal medication.—As might have been expected, when we consider the nature of this malady, almost every drug in the pharmacopoeia has been at one time or another tried in its treatment, but only those medicaments that are generally recognized as tonics have proved of real value.

First and foremost among these is *arsenic*, which was first recommended by Lombroso, and which has been used extensively by all pellagrologists for the last 50 years; among those who have testified to its beneficial effect are Lombroso (11), Casali, Cremaschi, Strina, Tibaldi (1), Gemma and Tosoni, Bennati, Camillis, DeOrchi, Majocchi (2), Galli, Babes (1), Ghirardini (3), Alpago-Novello, and a host of others. As a general rule the drug has been given in the form of arsenious acid or Fowler's solution; when the latter form is chosen the medicament should be administered in ascending doses, begin-

ning with three drops three times a day and increasing a drop a day until finally the point of tolerance is reached; in many cases patients take from fifteen to thirty drops three times a day without ill effect. Within recent years many of the newer arsenical compounds have been used, as, for example, Galli recommends *arsenate of iron,* Camillis the *albuminate of arsenic,* while still more recently *atoxyl* has been advocated by Babes (1), and Babes and Vasiliu, Ghirardini (3), and many others, and the *cacodylate of soda* by Fabbri; both of these drugs have been largely used in the United States, but it does not appear from what statistics we possess that the results have been particularly encouraging. With the false idea that arsenic acts in a specific way in this disease, many American physicians have given *salvarsan,* with results that of course must necessarily be of no particular value, though it is doubtless the case that in many patients the annoying symptoms have disappeared after its use, just as they would have done had the drug been omitted; however, the dangers connected with the administration of this substance are sufficiently real, and accidents have occurred often enough to warn him who would do the best for his patients to abstain from its use. Agostini observes that arsenic should not be given in the early stages of pellagra where there are symptoms of stomach irritation.

Formerly *lead acetate* was advocated by Lombroso, Cremaschi, and others, but in recent years its use has been generally abandoned.

Among other tonics that have been advised are *nux vomica* or *strychnine, iron, quinine,* and *Peruvian bark.*

Fabbri has particularly recommended Merck's *ammoniacal citrate of iron,* which may be given hypodermatically either alone or in combination with *glycero-phosphate of soda* and *nitrate of strychnine.*

Brunati affirms that a mixture of extract or tincture of *Peruvian bark* and *Fowler's solution* is particularly efficacious,—the arsenic being better borne in such combination than when given in any other way.

Recently Law has thought that he observed beneficial results follow the use of tablets of *Bulgarian lactic acid bacilli,* each containing seven and a half grains, and administered a half hour before meals.

From the time of Gherardini alcohol has been recommended in pellagra, and while it is not now so commonly advised as formerly many competent authorities still cling to it; thus we find that Tibaldi and Danielli laud its good effect; the first named giving it as wine, the last two as either wine or brandy in such amount daily as would contain from one to one and a third ounces of alcohol.

In that type of pellagra where symptoms of Addison's disease predominate both Bertelli and Rubinato have seen pronounced effects from adrenalin,—the former claiming to have cured two cases in this way. This is in keeping with the good effects of adrenalin and alcoholic extracts of cabbage leaves noted by Rondoni (2) in animals which had become disease from an exclusize maize diet.

Daily application of *faradic electricity* to the muscles has been thought beneficial by some.

Lombroso (11) has recommended rubbing the body with salt, especially in the hereditary forms of the disease.

Attention should be especially directed to the fact that many early writers were of the opinion that the use of salt is of value in the prophylaxis and treatment of pellagra. This view was particularly urged by Morelli, and has been later shown by Camurri (2, 8) to have a scientific basis, since he has demonstrated that in pellagra there is a gradual loss of all of the mineral salts.

Transfusion.—Transfusion has been more or less employed in the treatment of pellagra for the last thirty or forty years, appearing to have been first recommended in 1874 by Tamburini (1), who however employed lamb's blood for this purpose. Some years later the subject was again referred to by G. B. Verga (1), who asserted that transfusion had been frequently employed, but that no permanent results followed its use. The matter was also discussed by Berger, who expressed a similar opinion.

More recently this process has been rediscovered in America by Cole, of Mobile, who has written several interesting papers on the subject, both alone, and in connection with Gilman and Winthrop. The process has likewise been practiced to a considerable extent by southern physicians, with such results as might be expected under the circumstances. Inasmuch as this procedure is usually carried out in the very severe forms of the malady, where the patient is anaemic and highly toxic, more or less temporary improvement naturally follows, but the author has never in any instance seen anything more accomplished than is brought about by hypodermoclysis. The history of such cases seems usually to be that patients are as a rule greatly improved for a time, but that the pathologic alterations are already of too severe a nature to permit of any measure proving of permanent advantage. Of this the case recorded by Tamburini seems typical; the patient was evidently in a hopeless state at the time the first transfusion was carried out, and was for a time wonderfully improved, though death ultimately occurred on the forty-sixth day after the first injection. In the earliest stages of mental symptoms transfusion may perhaps prove to be of much more value than in the more extreme cases where it has in the past been generally employed; it is possible also that in some cases of typhoid pellagra life may be prolonged for a considerable period by this method of treatment.

Even at late as 1899 Anacleto claimed great benefit in this disease from bloodletting, taking as much as from 200 to 400 c.c. (6½ to 13 ozs.) in strong and 50 c.c. (2-3 ozs.) in weak individuals every three or four weeks, repeated several times.

Hypodermoclysis.—Hypodermoclysis has likewise been employed much within recent years in the treatment of the severer forms of pellagra, though, as is the case with transfusion, it can never be hoped that by this means the patients can be actually cured. Perhaps the most favorable of the results that may be hoped for from it are those that are said by Talasescu to follow its use in the earlier stages of the pellagrous insanities. Antonini (6) likewise strongly

advocates this procedure in the graver forms of pellagra; he injects 100 to 150 c.c. of a physiologic salt solution beneath the skin, and repeats as often as indications demand. The good results of hypodermoclysis are of interest in connection with the old idea just referred to that salt is beneficial in pellagra.

In by no means rare instances where acidosis occurs intravenous injections of *sodium carbonate* are of great value, —about one ounce of the drug to a quart of water; great care must be exercised to prevent the solution from getting into the tissues surrounding the vessel as it will cause sloughs. At the same time subcutaneous injections of *glucose* should be administered, the amount at one time being one quart of normal salt solution containing 10 per cent. of the medicament. Alkalies and carbohydrates should also be given by mouth.

Serum therapy.—Within recent years a number of attempts have been made to discover antitoxines for pellagra, and the subject is still being vigorously investigated, notwithstanding the fact that a proper understanding of the nature of the anatomical lesions of this malady would seem to preclude entirely the possibility of any agent ever being found that would in reality effect a cure.

Among those who first worked in this connection may be mentioned Antonini and Mariani (2), who based their hope of producing an antitoxin on some work done by Babes and Manicatide, and later by De Pietro (2); these investigators, as already mentioned, made the curious observation that while maize poisons produce death quickly when administered subcutaneously to animals, they are harmless when injected along with the serum of the blood of a person who has apparently recovered from pellagra. Antonini and Mariani (2) further showed that the toxicity of the blood of an active pellagrin is neutralized by the serum of a person apparently cured of this disease, and that this action is quite apparent *intra vitam* when the serum is injected into persons suffering from this malady,—there being exerted under such circumstances an antidotal effect; similarly they show that the blood serum of a goat poisoned with the toxines of bad maize exercises an antitoxic action on the serum of active pellagrins. In criticism of the results obtained by these writers it may be remarked that they only treated four cases in the human being, and that it is impossible from such a small number to draw any general conclusions of value.

More recently Gatti (1) has treated a couple of cases in a similar way, both being severe, and recovery occurred in one instance.

Latterly a good deal has been written about a "serum" devised by Nicolaidi (1, 2); this medicament is called by its originator "an organo-polymineralized radio-activated serum," but what the stuff really is no one except its originator appears to know,—he having refrained from explaining its method of manufacture, so far as the author has been able to discover, though he states that a full report of his researches is being prepared, and will be given to the world later. From what little is said concerning this "serum" it would appear

that it is not a serum at all, but that it consists of a solution of various salts which the bodies of pellagrins, as shown by Camurri, more or less lack, and that it is rendered radio-active by radium or some similar substance. Quite a number of cases appear to have been treated by this method, there having been papers written on the subject by Grillo and Maj, Blanchard and Sozzo, in addition to a number of communications by Nicolaidi. While it is not impossible that the more acute processes that occur in this disease may be in some instances influenced by Nicolaidi's "serum," it is of course perfectly clear that to it, no more than to other methods of treatment, could we look for a permanent cure. It is not improbable that its effects will be found much the same as those secured by hypodermoclysis.

GASTROINTESTINAL SYMPTOMS.—The treatment of the gastrointestinal symptoms will of course depend on their nature and severity.

Mouth and throat.—Where lesions develop on the lips, tongue, gums, buccal mucous membrane and throat all methods of treatment heretofore devised are unfortunately of but little avail. Under such circumstances the patient should of course *limit himself to a perfectly bland diet,* such as milk or raw eggs, and the mouth should be washed out from time to time with *soothing, mild antiseptic solutions.* Where actual ulceration has developed the author has never been able to convince himself that drugs exert any marked influence over the process. Walker, however, states that he has seen undoubted improvement quickly follow applications of *nitrate of silver,* and this should undoubtedly be tried. In some instances the author has thought that betterment followed after the parts were treated with applications of *tincture of iodine.*

Stomach.—Where the disease has progressed sufficiently to cause decrease or absence of the gastric juice it is thought by Fabbri that washing the stomach out with salt solutions is of benefit. Camillis has also recommended under such circumstances the *sulphides,* on account of their supposed action in favorably influencing the gastric secretion.

Intestines.—For the intestinal disturbances rest in bed and a milk diet are absolutely essential, and must always form the basis of any rational treatment of this complication. The silver salts have been recently used internally with some success, *protargol* having been particularly recommended by Boscolo-Bragadin, and later lauded by D'Ormea (3), Fabbri and others. The dose recommended is from one to three grams (15 to 45 grains) daily, depending on the intensity of the process; the drug is best given in wafers.

Likewise *opium* and *astringents* have been frequently employed in the treatment of these conditions, though by no means always with success.

The following formula was originally devised by Lombroso, and later highly lauded by Gemma (4) in the treatment of dysenteric complications:

Hydrarg. chlor. mit.	gr.	2.3
Pulv. opii	gr.	0.6
Sacchari	℥	ss.

μ. et ft. pulv. No. XVI
Sig. One every 2 hours.

Among the astringents that have been recommended are the salts of *bismuth, zinc, tannic acid,* etc.

Alpago-Novello (1) recommends the following:

Bismuthi subnitratis			
Zinci oxidi	aa	ʒ	2.5
Ac. tannici		ʒ	1.4
Pulv. opii		gr.	3.8

μ. et ft. pulv. No. XXX
Sig. One every 2 hours.

Colon lavage has also been recommended in the treatment of pellagrous diarrhoeas by Gemma (10). He dissolves from 1.5 to 2 drams of carbolic acid in three quarts of water and injects 300 to 500 c.c. of this solution twice daily.

SKIN SYMPTOMS.—For the skin complication of pellagra no abortive method of treatment is known.

As a local treatment Majocchi (2) recommends for the lighter forms Hebra's *glycerolate ointment,* and *antiseptic applications* in the more pronounced lesions accompanied by the formation of blebs and ulcers.

Merk (2), while admitting that we have no therapeutic agents that prevent the development of pellagraderms, notwithstanding believes that much may be accomplished in the way of preventing secondary infections, and thus materially shortening the course and mitigating the severity of these complications.

First and foremost he recommends cleanliness, and says the parts should be thoroughly washed daily with soap and warm water.

When the lesions show marked inflammatory changes he advises compresses saturated with solutions of *acetate of aluminium* of a strength of about 1 per cent.; the application should be changed every four hours, day and night, without the whole is well covered with a rubber dam, in which case this would only have to be done once or twice a day. It is usually unnecessary to keep up the use of the compresses longer than three or four days.

Where the inflammation is very severe the application of *ice* over the part is oftentimes very grateful, and is even of value in reducing the severity of the process.

If the skin lesions are from the beginning of moderate severity, or if the treatment just referred to has produced marked amelioration in more severe forms of the trouble, the further treatment con-

sists in washing the parts frequently, and then covering them with a salve composed of ten parts each of *boric acid* and *glycerine,* rubbed up in 100 parts of simple ointment; this salve is spread over the diseased area in a thin layer, and is then covered with a mixture of equal portions of *oxide of zinc* and *talcum powder.* This method of treatment has the advantage that it is not necessary to bandage the parts after the ointment has been applied; if the patient so desires, the powder may be colored with *bolus rubra* in sufficient amount to give it a flesh tint, thus making it less conspicuous.

If bullae or ulcers have already formed when the patient is first seen, all dead skin and scabs should be washed away and the part covered with *aluminium acetate* compresses, as before directed.

NERVOUS SYMPTOMS.—The nervous symptoms of pellagra must be treated on general principles. On account of the fact that the mentality is always more or less affected, these patients are usually quite susceptible to the action of drugs that particularly act on the higher nerve centers, and when administered must be watched with great care. As sedatives *bromides* are occasionally of some use, but are not as a rule sufficiently powerful to produce marked effects. For high degrees of nervousness and sleeplessness it is usually necessary to employ the more powerful hypnotics, such as *luminol, adalin, veronol, sulphonol,* or *trionol. Opium* is usually not very satisfactory with these patients, as its use is often followed by a wandering delirium, which may deepen into coma and finally end in death. For the *vertigo,* which is such a common symptom of this disease, Lombroso has recommended *Coculus orientalis,* a preparation which is described in the homeopathic pharmacopoeia.

MENTAL SYMPTOMS.—The mental symptoms of pellagra are best treated by *rest in bed, abundant nourishing food, and careful nursing.* If looked after properly in the earlier stages the mental symptoms usually subside in from one to three months. *Hypodermoclysis* is said to be followed by excellent results in many cases if begun early.

In the hereditary forms of the malady Lombroso (11) has highly recommended daily frictions of the entire body with common salt.

TYPHOID PELLAGRA.—It is generally agreed by authorities that there are few complications in any disease of greater gravity than that *ensemble* of symptoms designated by the term "typhoid pellagra," though writers differ in their statistics as to the mortality; doubtless this is due to just what symptoms are thought to constitute this complication. There can be no doubt that recovery is very rare where the patients exhibit all of the classical symptoms of this variety of the disease.

Antonini (6) speaks well of *hypodermoclysis* in its treatment, and cases of recovery have been reported after the use of *serum from pellagrins who had apparently recovered;* likewise Nicolaidi's "serum" is alleged to have produced very favorable results in some instances. Generally speaking all that can be done under the circumstances is to treat the patient symptomatically.

TREATMENT IN CHILDREN.—The treatment of pellagra in children varies in no important particular from that of adults. The like remark is true respecting the conditions that are regarded as hereditary pellagra. Children manifesting symptoms indicating that they are the victims of this disease, in whatever form it may occur, should however be given very special care during infancy and childhood. Wherever possible they should be placed in institutions where they can be properly looked after, and should be given nourishing food, and they should spend their entire time in the open, and be encouraged in every way to develop the physical side of their being. It is even more necessary than with normal children that they be kept as long as possible out of school, and should rarely if ever be permitted to begin their mental education until after the age of puberty is well passed. For them, as for older pellagrins, the best treatment consists in complete abstinence from maize products, whether mouldy or not, an abundant supply of good and nourishing food, and proper hygienic surroundings.

Caldana and Lucatello have recently urged institutional treatment for children showing signs of hereditary pellagra, urging, with truth, that it is much better to eradicate the seeds of this terrible malady in youth than to try to cure them after the disease has fully developed in later life; they apparently cured 46.15 per cent. and greatly improved 44.23 per cent. of a large number of cases treated.

CHAPTER IX

THE RELATIONSHIP OF PELLAGRA TO LIFE INSURANCE.

While the space-limitations of this volume are too restricted to permit anything like an extensive discussion of the relationship of pellagra to life insurance, the author, nevertheless, feels that the subject is of too much importance to be entirely ignored.

So far as he is aware none of the life insurance companies have at yet incorporated in their applications for policies questions having as their object an attempt to disclose as to whether or not pellagra had likely occurred in any of the immediate relatives of the applicant, nor are the examiners required to make the physical examinations necessary to establish the presence or absence of this disease in such persons. That this omission is a serious one all will admit who have any knowledge of the extraordinary fatality that attends this horrible affection, and who have any conception of its frequency in the southern portions of the United States. While we have neither comprehensive nor accurate statistics on morbidity and mortality in this region, we, nevertheless, have fairly accurate figures as respects the causes of death in many of the towns, and it will be found on perusal that pellagra is one of the three most fatal of all diseases in this region. When it is remembered that unquestionably a great many people die of obscure forms of pellagra, and are consequently not counted as among those who have perished of this affection, and when it is considered that the mortality from his disease is certainly lower in cities than in the rural districts, we cannot escape the conclusion that in all probability this murderous malady is at the present time the most frequent cause of death over a large area of the southern portions of this country. Under such conditions it is only fair to those who are not affected with this disease, as well as to the life insurance companies themselves, that some sort of cognizance be taken of this distressing situation, and the subject should undoubtedly receive the immediate and earnest attention of those whose duties are to look after such matters.

Inasmuch as it has been shown beyond the shadow of a doubt that this affection is hereditary, the offspring of pellagrins should not be insured on the same basis as persons of better ancestry. It is furthermore in the highest degree important that a series of questions

be formulated which would have as their purpose the determining as to whether the applicants have the more typical manifestations of this malady, and—of quite as much importance—the examiner should carefully search for physical evidences indicating a pellagrous taint, such as anomalies and deformities, particularly about the head and face, the marbled and bluish appearance of the mucous membranes, the sulci in the tongue, the numerous peculiar skin changes, and the altered reflexes, all of which are so common in the earlier stages of the affection, and make inquiries as to constipation, flurries of diarrhoea, weakness—especially of the legs—burning sensations in the feet, hands or intestinal tract, vertigo and general depression, most of which symptoms are greatly increased in the spring and early summer.

The author has been authoritatively informed within recent years that many of the sick benefit and accident insurance companies have actually lost, instead of having made, money in the south within recent years, and that this is to a lesser degree true of life insurance companies he has also been told. A proper adjustment of this situation can only be brought about by a recognition of the tremendous rôle that this affection plays in both the morbidity and mortality in the southern states, and is a matter, therefore, which deserves the most careful consideration of everyone interested in this subject.

APPENDIX

"RUN OUT" CONDITION, POOR GERMINATION AND ROTTING OF INDIAN CORN.

By Prof. P. O. Vanatter, of the Georgia State College of Agriculture.

Few people realize the value of the maize crop of the United States. The yield in 1910, according to the Yearbook of Agriculture, was 3,125,713,000 bushels, valued at $1,523,968,000.00. This is a little more than twice the value placed on any other crop produced in the United States.

The whole country, therefore, is interested in this cereal, for a slight increase or decrease in yield per acre affects nearly the whole commercial industry of the nation. It is all-important, therefore, that this crop, which means so much to the welfare of the whole country, should be handled in the most careful and scientific manner in every respect, for if improper methods are adopted in the breeding or handling of the grain the loss may amount to millions of dollars in a single season. It might be well, therefore, to stop occasionally and consider if the present system of breeding, cultivation and handling the crop is bringing the results that should naturally be expected of it.

Indian corn of low vitality.—It is pretty generally admitted that this cereal, as a general rule, is of low vitality. Professor P. G. Holden, one of the best experts in scientific maize growing, writing in the 15th Biennial Report of the Kansas State Board of Agriculture, for 1905 and 1906, has the following to say about the condition of this crop in the state of Iowa:

"The fact is that bad seed corn has cost Iowa this year not less than 60,000,000 or 70,000,000 bushels of corn." "This," he says, "is putting it at the very lowest possible limit. Few people realize how great is this loss to the state each year. Last winter and spring something more than 3,300 samples of seed corn were sent to the Agricultural College at Ames to be tested. These samples came from every section of the state and were made up in each case of 200 kernels taken from 100 ears, thus giving a representative sample of each man's seed. The samples were given a careful germination test with the following results:

	Per cent Germination.		
Average of 20 samples	Strong	Weak	Gave no germination
taken at random.	58.20	21.8	20

The *Farmers Advocate,* April 4th, 1912, had the following article about the condition of seed in Iowa:

Poor Seed Corn.—"Just how serious the seed corn situation is in Iowa was demonstrated in an extensive test of farmers' seed corn conducted at Mason City recently by a representative of the Iowa State College."

"Of one thousand ears coming from ten different farmers where they had been selected and set aside for seed because they seemed outwardly to be the best, only 311 contained no dead kernls, and were, therefore, fit for planting. In one lot of 100 ears not a single ear fit for seed was found. In two other lots of 100 ears each only 17 good ears were found in each. In a fourth lot of 100 ears only 20 were fit for seed. The best lot of 100 ears yielded only 58 good ears for planting. These tested ears were not common ears; they were brought in for testing by reasonably careful farmers who selected their seed in the field last fall and took reasonable care of it through the winter. Probably they represented 1,000 of the best ears available on ten representative farms. The cost of planting corn like that can not be estimated. Prof. M. L. Mosher, of the extension department of the college, and an expert in corn, says that to plant such seed as tested at Mason City would mean a reduction of probably 20 bushels per acre in the yield. 'That is just an approximation, of course,' said Mr. Mosher. 'In an average year, covering all sections of Iowa, we find that the seed corn used has about 12 per cent dead kernels. That average is based on the test of 3,500 samples taken through a series of years in various sections taken from planter boxes. In an average year this 12 per cent seed corn grown under good conditions produced 57 bushels per acre. Taking those averages as a basis, this Mason City corn which is 40 per cent dead would produce not more than 35 bushels per acre if grown under most favorable conditions. The 1,000 ears in the first Mason City test are not poorer than the average.

"I have just received a report of the second testing of seven lots of 100 ears. In one lot, taken from the crib, not a single kernel of the 100 ears germinated. In a second lot of 100 ears only one ear was without dead kernels, and in a third only eight. The lots, on the whole, were far worse than those of the first test. I believe that farmers near Mason City are "up against it" for seed corn.

"The college is active with preparation for the seed corn trains which will run over the lines of the Burlington and Rock Island Railways in Iowa in the next few weeks. It is also distributing 100,000 pieces of seed corn testing literature through its own mailing lists and through commercial clubs and business men to which it is furnishing these bulletins free."

These articles on the condition of maize seed in Iowa were written by responsible men who were specialists in their line. They show very plainly the problem that confronts the people in this section of the country in securing good seed. The leading prolific varieties in the state of Georgia germinate much better than the Iowa samples here described, as well as many other samples tested from different sections of the maize belt, but this can not be said for the large-eared non-prolific varieties grown in this state.

No Indian corn ever produces perfect germination.—It may be a surprise to some to know that no variety of maize ever gives a perfect permination if ears are taken from plants just as they grow in the field. Even where choice ears of any variety are carefully selected for show purposes, if a comparatively large number are chosen, some will always show weakness in germination; if several varieties be tested it will be observed that some will germinate better than others, and if this test be kept up for several years it will be found that some seasons the vitality of the seed will be much worse than others.

Cause of low vitality.—The most popular belief, especially throughout the maize belt, is that this cereal spoils during bad spells of weather, while still in the shock, and that this also occurs where it is exposed to damp weather, freezing, etc. These things are undoubtedly responsible to a certain extent for the bad condition into which the grain often gets in this country, but the writer thinks that this is by no means the first and most important cause of its low vitality,—rather believing that this results from selecting and breeding according to score-card methods, without any reference to the vigor of the plants from which the ears come.

Storing seed maize.—The writer gathered choice ears from the field, before they had any chance to become affected by bad wather, and stored them under different conditions, such as in the barn, house, even in the kitchen during the winter, and, while the samples properly cared for germinated better in the spring than those stored in the barn where they were exposd to climatic changes, some ears always gave a better germination than others, no matter how they were protected.

What caused this difference in germination?—This has been the problem that the writer has been trying to solve now for several years, and as different samples produce varying results in the germination test no matter how they were selected and stored, a search has been kept up to find out, if possible, what caused this difference, and, while several years passed without a definite explanation, the results secured since 1909 have been very encouraging.

Choice ears from each of several different varieties are received yearly at the Georgia State College of Agricultur for use in the variety test. These ears have been carefully tested, and it has been found that some varieties always give better results than others. Comparing the germination with the yield each year, it was always found that the varieties that proved the weakest in the former were lowest in the latter particular. Whatley's Prolific, as received from the grower, has always germinated fairly well, while Red Cob germinates, as a rule, very poorly. Henry Grady comes between these two varieties. A comparison of these varieties for yield and germination is here presented:

Name of Variety	Yield per acre of grain bu.	Per cent Germination	
		Total	Strong
Whatley's Prolific	82.11	92	82
Henry Grady	57.80	87	74
Red Cob	49.51	60	37

These varieties were grown side by side in the field and had the same treatment in every respect. The per cent. germination is the average of ten ears from 10 highest yielding plants out of 20. These results, therefore, indicate that if we sow seed of a variety of maize that exhibits weak germination, the seed from the plant that follows will in turn present similar characteristics, showing that breeding affects the vigor of this cereal. Care was taken in this experiment not to allow the grain to become injured by bad weather, etc. The difference in germination, therefore, can not be charged to anything of this kind. How then can we account for this difference in vitality between these varieties? As they are all native the only conclusion that can be drawn is that various methods of selection and breeding has caused this difference. This experiment has been duplicated many times with different varieties and different strains of the same variety, and always with the same results.

Sappy condition of stalks.—After five weeks drying in the field in good weather the bare stalks of these same plants which produced the ears that were used in the germination test just described were compared for weight. The bare stalks from the 10 highest yielding plants of Whatley's Prolific variety averaged 9 ounces, while those of the Red Cob averaged 13. Now this same thing is true within a variety, as is shown by the fact that the better the yield of individual plants the quicker do these plants dry out after maturity. In this expermient the 10 plants of the Red Cob variety that averaged 13 ounces of bare stalk produced on the average 18.50 ounces of ears. These were the 10 highest-yielding plants out of 20 in the row. The average of the 10 lowest-yielding plants out of 20 in the row was 10.31 ounces of ears, while the average weight of the bare stalks from these low-yielding plants was 22.18 ounces as compared with 13 ounces for the highest-yielding plants of the same variety, and 9 for the highest-yielding

plants in the Whatley's Prolific. These experiments have been duplicated many times, and always with the same results.

Sappy condition of stalk may affect the ear.—There is no doubt that the failure of the stalks to dry out properly affects the ear, and the reader can see that this condition, along with bad weather while the grain is in the shock, would act more deleteriously on a poor variety, like Red Cob or Henry Grady, than on a good variety like Whatley's Prolific. The last named, of course, would be affected by bad weather while the corn is in the shock, but the reader will understand that, while Whatley's Prolific is more resistant to climatic conditions and is a better variety than the others here mentioned, it is by no means perfect. However, it would appear from these tests that the possibilities of selecting for still greater resistance are very great indeed, but this point will be made clearer later on.

"Run out" condition of maize.—The author believes that all varieties of Indian corn are in more or less of a "run out" condition. By this term is meant that the plants of any variety run from a high to a low yield, and if we take a very large number of plants we very nearly always find some, called "barren stalks," do not produce. Comparing different varieties at the college during the last three years, it has been found that they differ considerably in this respect. Twenty plants have been studied each year from 20 different varieties. Some have always had one or two plants out of 20 that did not produce, while others have never "run out" entirely during the last three years; without exception some plants have given very satisfactory results, but the yield gradually falls off until it becomes very low indeed in most cases. In 1911 ears were selected from 20 plants just as they grew in the field and placed in order of yield. The highest-yielding plant in the best-yielding variety was 38 ounces, while in the poorest-yielding variety it was only 28. The best variety gradually decreased in yield to 13 ounces for the 20th plant, while only 19 out of 20 produced in the poorest variety.

Rotten corn.—There was more rotten corn at the college than usual in 1911, and yet there was less rain than usual. It was found this year that in some varieties there was more rotten grain than in others. The one producing the best results was a good prolific, while that exhibiting the worst "run out" condition and having the most rotten corn was a non-prolific variety. It will also be noticed that in the lowest-yielding plants most rotting occurred in both varieties. Likewise it is in a poor variety that the stalks dry out with such great difficulty.

Why does maize rot worse in a dry season?—The drought in 1911 presented a fine opportunity for a study of this kind. Careful observation during this period revealed the fact that some plants were suffering much worse than others. The type of plant that stood the drought the best was the one which produced suckers. This may seem strange for it is generally thought that the suckers tend to exhaust the plant. It is true that some plants of this type suffered, but on the average they were much more resistant than the others. If anyone will take the trouble to examine different plants in the field just after a heavy rain, about tasseling time, they will find that the plants that have produced suckers are usually well rooted and can only be pulled up by employing much force, while rather a large per cent. of those that do not stool are easily moved about and are quite loose in the soil. Now it is interesting to observe that the latter suffered most during the drought, and were the low-yielding plants. In many cases the upper leaf and part of the tassel were entirely killed by the dry weather. It is evident that these low-yielding varieties and plants are constitutionally weak, and the yield suffers as a consequence. It is only in extreme cases where the ear actually rots, but the germination is always affected. The ears of these weak plants in 1911 often underwent a process of what is called "sweating" in the shuck, and in many cases rotting resulted.

"Run out" condition of different strains of the same variety.—This is shown in two strains of Whatley's Prolific grown in the breeding plat in 1910. This corn was grown at the rate of 4,000 plants per acre. Ears

were selected from 20 plants just as they grew in the field and placed in order of yield. It will be noticed that the highest-yielding plant in the best-yielding strain gave a yield of 53 ounces or 230 bushels per acre, while the highest-yielding plant in the poorest-yielding strain made a yield of 39 ounces or 174 bushels per acre. The best strain gradually decreased in yield to 8 ounces for the 20th plant, while the yield for the poorest-yielding strain only showed 5.5 ounces for the 19th plant, there being one that did not produce at all.

Ear No. 4 gave an average yield of 116.25 bushels with 90 per cent. germination, while Ear No. 54 gave an average yield of only 84.56 bushels with 75 per cent. germination. The same thing is found to be true here as for the best-yielding varieties, the best-yielding strain producing the highest per cent. germination. Here again if we shock the product of two strains in the field during a spell of bad weather, it is found that the strain in the worse "run out" condition is not so resistant to climatic conditions as the better one.

The same thing can be said of the low-yielding plants in a strain or variety. Suppose we compare plants 1 to 10 with plants 11 to 20 for germination, etc.; it is found that the ears from the high-yielding plants give the best germination, etc. For the last three years this experiment has been carried out in detail for 20 different varieties, and with many different strains, and the same thing has always been found to be true, viz., that the highest-yielding plants on the average always give the best germination. To make this point perfectly clear the results of a germination test between high and low-yielding plants for 10 varieties, grown in 1911, are here presented:

Name of Variety	Average yield per acre of grain bushel.	Average weight, ozs.		Average per cent. germination			
		10 highest yielding plants out of 20	10 lowest yielding plants out of 20	10 highest yielding plants out of 20		10 lowest yielding plants out of 20	
				Total	Strong	Total	Strong
Whatley's Prolific ..	42.47	16.48	10.70	83	60	67	48
Hasting's Prolific ..	43.24	13.75	9.30	95	72	97	69
Vinson's Prolific ...	49.97	16.56	12.72	88	60	83	49
Marlborough Prolific.	37.06	13.23	8.55	76	39	61	25
Spark's Prolific	42.15	13.90	9.51	91	69	62	44
Average	42.98	14.78	10.17	87	60	74	47
Shaw's Improved ...	33.90	12.26	6.00	86	69	51	29
Henry Grady	34.35	11.63	7.50	44	15	47	10
Welchel's Dent	34.86	11.50	5.93	63	42	59	22
Huffman	36.84	12.33	7.41	76	55	53	37
Red Cobb	34.83	12.40	9.62	66	40	54	10
Average	34.96	12.02	7.29	67	44	53	22

In this table we have five prolific and five non-prolific varieties of maize. It will be seen that the prolific varieties are in the lead both as to yield and

germination. The difference in germination between the 10 highets and 10 lowest-yielding plants is also very marked. The low average yield and per cent. germination of the varieties shown in the above table can not be materially bettered by any methods of handling the crop, but this can be accomplished by intelligent breeding covering a period of many years.

The acidity of corn.—The acidity test that is now used in Italy and Austria to determine the fitness of maize or its products as a food for man or beast is attracting a great deal of attention all over this country. All Indian corn, it seems, is naturally slightly acid, but when it becomes mouldy it develops still greater acidity, and on this score it is often condemned. What puzzles many is the fact that perfectly good-looking corn, so far as the miller or farmer can judge, may be condemned on this score and classed as rotten. It is this kind of maize that is believed by almost all authorities to be the cause of the dreadful disease called pellagra. As soon as the writer learned of the acidity test for fermentation in the ears that came from the low-yielding plants, and investigation showed that the grain from these low-yielding plants not only exhibit poor germination, but develop much more acid than the more vigorous strains of this cereal.

Acidity number of sound corn.—In all about 50 samples have been tested for acidity by the Department of Chemistry, Georgia State College of Agriculture.

The first test was between the highest and lowest-yielding plants out of 20 under examination. The average results of these tests are as follows:

Average..... { High-yielding plants, 23.81 c.c. acidity
Low-yielding plants, 37.06 c.c. acidity

In most cases the ears from these low-yielding plants appeared to be perfectly sound. There were one or two cases, however, where the ear from the low-yielding plant was partly rotten, and wherever this happened to be the case the acidity ran very high. In one case a small partly rotten ear from a low-yielding plant went as high as 68 c.c. acidity, while the two good ears from the highest-yielding plant only showed 17 c.c. In another case it was 24 c.c. acidity for sound ears from the highest-yielding plants, while a partly rotten ear from the lowest-yielding plant showed 48 c.c. Where both ears were sound the results were as follows:

Name of Variety	Description and Source of Variety	Description of Plant from which Sample was taken	C. C. Acidity
Whatley's Prolific ..	A good type of a Southern prolific variety	Highest yielding	13.00
		Lowest yielding	17.50
Huffman	A good type of a non-prolific Southern variety	Highest yielding	21.00
		Lowest yielding	28.00
Funk's Yellow Dent..	A good type of a Western variety	Highest yielding	36.00
		Lowest yielding	55.00

Taking the average of the 10 highest and 10 lowest-yielding plants out of 20 for these varieties, and from the same lot that the samples were taken for the acidity test, the germination was found to be as follows:

Whatley's Prolific.. { 10 highest yielding plants out of 20=83% total germination
10 lowest yielding plants out of 20=67% total germination

Huffman..... { 10 highest yielding plants out of 20=76% total germination
10 lowest yielding plants out of 20=53% total germination

Funk's Yellow Dent. { 10 highest yielding plants out of 20=30% total germination
10 lowest yielding plants out of 20=05% total germination

These results go to show that poor germination and high per cent. of acid are very closely related, and, no doubt, therefore, the same condition that causes the former is responsible for the latter. In a more favorable season, however, it is not likely that there would be as great a difference in acidity between these several type-plants.

Other examinations for acidity were made of choice ears of several different varieties received direct from the grower to be used for the variety test at this place; these ears were given a careful germination test and then divided into two lots: first, those showing the strongest, and, second, those the weakest vitality. Samples from both were then tested for acidity, with the following results:

Average..... { Sample from ears showing strongest germination 18.66 c.c. acidity
Sample from ears showing weakest germination 23.66 c.c. acidity

Now, if ears of corn from low-yielding varieties, low-yielding strains of the same variety, and low-yielding plants produce poor germination, and tend to develop too much acid, etc., then there must be some standard of yield that maize should make before we can expect it to give a good account of itself in the germination and acidity tests.

At present it is quite a popular belief that an ear of Indian corn that is of standard size, shape, etc., is unexceptionable, and the average yield of all plants in the row is seldom if ever taken into account. Everybody who has visited any of the large maize shows of the United States has admired the fine exhibits. The grain has been selected and bred in many cases until it would seem that so far as the shape of the ear is concerned there is little or no room for further improvement. The non-prolific varieties grown in the State of Georgia, in many cases at least, are no exception to this rule. In fact, some of them have taken prizes at the National Corn Show, and, while they are as pretty as a picture to look at, they show up to disadvantage when it comes to comparing them for strong vitality, yield, etc., with the leading prolific varieties of this section,—which are not being selected and bred according to show and score card standards. (See comparison of prolific and non-prolific varieties in another place in this paper).

According to the idea that has been here developed, maize should not only be selected for properly shaped ears, but also for high yield. It is also true that the ears from a few high-yielding plants in the row will not bring the desired results, as much imperfect grain is always present where the general average is not good. No matter under what condition maize is grown there seems to be a certain standard for yield that a variety should reach before it will give a good account of itself in the germination test, etc. This standard, of course, will vary from year to year, and for every farm in a county or state.

In 1911 the land was not so well suited for this cereal as that employed for this purpose in 1910, nor was it as well prepared; besides, there was no rain for two months after the plant was up, and very little after this time, so that the crop had very severe conditions to meet in 1911. The average yield per plant for the highest-yielding variety was 11.52 ounces, while the average yield for the poorest-yielding variety was 9.75 ounces. A variety, or strain of any variety, which would not make a higher average yield per plant than 11.52 ounces, grown under conditions similar to those experienced in 1910 would be so poor as a rule that it would be absolutely unfit to feed to man or beast, providing all varieties matured about the same time. Yet, 11.52 ounces seemed to be a very good standard for the conditions under which the corn was grown in 1911.

The poorest-yielding variety gave an average yield per plant of 9.75 ounces, or 1.77 ounces on the average per plant less than the better-yielding variety. Here again we find the variety that fell below the standard has produced much more rotten grain than that which gave a better yield. The per cent. germination of these two varieties is as follows: The ears from the 10 highest-yielding plants in the best-yielding variety was 95 total, and 75 strong, while the ears

from the 10 lowest-yielding plants averaged 95 per cent. total, and 69 per cent. strong germination. For the poorest-yielding variety the results of the germination test were as follows: The average per cent. germination for the 10 highest-yielding plants was 66 total and 40 strong, while the 10 lowest-yielding plants only geminated 54 per cent. total and 10 per cent. strong germination.

Fine ears from poor strain or variety.—It frequently happens that the finest ears are to be found in the poorest-yielding strain or variety. This was the case with Ear No. 54. This strain averaged 2.94 ounces of ears less per plant than Ear No. 4, yet as far as fine looking ears was concerned Ear No. 54 had greatly the advantage.

High-yielding plants in poor strain.—20 per cent. of the plants in Ear No. 54 gave a yield of over 100 bushels per acre, while as many more went as high as 90 bushels per acre, and if there is anything in high yields producing good results we would naturally expect it from these high-yielding plants, but as stated before the general average is too low.

The reader may wonder how the poorest-yielding strain often produces the finest looking ears; the explanation of this seems to be as follows: The best-yielding strain of any variety at this place has always been the most vigorous stooler, indicating a more vigorous plant. There were 13 plants out of 20 in Ear No. 4 that stooled and produced ears on the stools, while only 8 plants out of 20 from Ear No. 54 stooled and produced ears on the stools. Now plants in No. 54 that did not usually stool produced two good ears of corn. When we take plants from Ear No. 4 that has produced not only two ears on the main plant, but also two or more stools with one or two ears each, it will be found that these ears as a rule are not quite so fine to look at, yet strange to say they will produce the best germination, etc. It may be said just here that stooling in the minds of most maize growers is a great objection, and the tendency all along has been to breed away from this type of plant, and the writer believes that just to the extent that a breeder has succeeded in accomplishing this purpose just so much has he lowered the vitality of the cereal; at least this seems to be true for the different varieties of maize tested at this place during the last three years.

Stooling of varieties.—Twenty varieties of maize were tested in 1910 for germination, stooling, etc.,—the year being favorable for the formation of suckers. The prolific varieties were the leaders in this respect, there being 13 plants out of 20 and in the non-prolific varieties 5 to 6 out of 20 that stooled. The plants were placed in three groups: 1st. Those that did not stool; 2nd. Those that stooled but did not produce ears on the stools, and 3rd, Those that stooled and produced ears on the stools. In every case, without one single exception, the ears that came from the group of plants that stooled and produced ears on the stools produced the best germination, the group that stooled but did not produce ears on the stools the next best, and the group that did not stool the poorest germination.

When conditions do not favor stooling.—When conditions do not favor stooling all we have to guide us in making intelligent selections is the yield per stalk, for a plant that produces well under these circumstances would be a vigorous stooler under more favorable conditions.

This experiment has also been carried out with many strains of corn of the same variety, and always with the same result. These plants that do not stool under conditions where, say from 30 to 65 per cent. of the plants stool, are easier blown down; they are less resistant to drought, they are poorer yielders, and do not produce as sound grain as the other type of plant; it is the stalks from such varieties that are so hard to dry out, etc. Now, if the author is right about the cause of poor germination of maize—and tests too numerous to mention seem to justify this conclusion in the matter—then the vitality of Indian corn in this country can be improved only by a careful use of the best varieties and by selecting and breeding only from high-yielding, vigorous plants of the right type.

AUSTRIAN LAW ON BAD MAIZE AND PELLAGRA.

Regulations respecting the eradication of pellagra, becoming the law on and after the 24th of February, 1904.

With the advice and consent of the parliament of my princely earldom of Tyrol, I hereby decree as follows:

Section 1. In the domains of the princely earldom of Tyrol, where pellagra prevails, the following regulations are hereby ordered, with the object of bettering the sanitary conditions of the people living within its domains.

These regulations are as follows:

(1) The erection and the support of local sanitariums.

(2) The erection and support of ovens for drying maize, and houses for its proper storage.

(3) The support of maize warehouses, in which good maize, and maize products, will be sold to the people, and spoiled or damaged maize products may be exchanged for good ones.

(4) The promotion of bakeries which will be operated by the municipalities in each district.

(5) The erection and maintenance of pellagrosari, and of supplementary hospitals for those ill of pellagra.

(6) The promotion of the locating of physicians in those pellagra afflicted districts where there are not enough doctors to meet the demand.

(7) The teaching of the people concerning the nature of pellagra, and the means necessary to combat it.

(8) The obtaining of pellagra statistics.

(9) The publication and the awarding of prizes for scientific work and meritorious investigation concerning pellagra, and methods of combatting it.

(10) The promotion of better agriculture, of industrial enterprises, and of public works in these districts.

The "pellagrous districts" include all those portions of the country which the governor shall so declare.

Section 2. To meet the cost of the regulations designated in Section 1, a pellagra fund shall be created, which shall be supported by equal contributions from the state and the affected provinces, the money to be supplied by taxes collected in a lawful manner, and through other resources. (No information is given of the source from which the last named funds may be derived).

Section 3. The governor, in conjunction with the provincial parliament, is empowered to make the necessary appropriations from this pellagra fund, and to carry out the provisions mentioned under Section 1. The estimates of the necessary sums to be appropriated from the pellagra fund shall receive the sanction of the provincial parliament, and that of the minister of the interior.

A pellagra commission is hereby created, the province of which shall be to consult with, and give information concerning, those subjects mentioned under Section 1. The governor, or a substitute appointed by him, shall sit as the president of this commission, and direct its discussions. This commission shall consist of the following persons:

(1) Three representatives from the provincial parliament.

(2) Two members shall be designated by the governor.

(3) One member from Section II. of the Provincial Council of Agriculture.

(4) A delegate shall be named from the chamber of commerce of Rivereto

(5) One member from the medical faculty of the University of Innsbruck.

(6) The provincial inspector of sanitation (particularly of pellagra), created by Paragraph 1, Section 5, of the law of the 5th of January, 1896, to overlook and inspect the sanitary condition of the pellagrous territory, shall also be a member of the commission.

(7) A member shall also be sent as a delegate by the Provincial Council of Hygiene.

(8) The medical society of Trient shall also appoint two of its members as delegates to this commission. The president shall have the power to appoint either temporarily, or permanently, persons, whom he may consider as having a special knowledge of this subject as extraordinary members of the commission.

The extraordinary members shall have the privilege of the floor at all meetings, but will not be permitted to vote.

Section 4. Concerning the carrying out of the more important regulations, such as are found in Section 1 of this law, the governor shall consult the judgment of the Commission. The Commission shall also have the power of creating other regulations, on their own initiative, when they deem them necessary. The business of the Commission shall be carried out according to rules made by the governor in conjunction with the provincial parliament.

Section 5. The Commission shall assemble in Innsbruck. Members who do not reside in this city shall have the expenses of their journey paid from the pellagra fund, these expenses being subject to revision by the governor, in conjunction with the provincial parliament.

Section 6. The state authorities are required to coöperate in the execution of this law. The magistrates are required to coöperate with the police in the carrying out of this law.

Section 7. The local health officers are required in their respective districts to coöperate with the police in the carrying out of this law, particularly in supervising the various institutions mentioned in Section 1, Paragraphs 1 to 5.

The local health officers are further compelled to report to the police all cases of pellagra of which they may know, and likewise the death of any one the prey of this disease.

Section 8. The health officers who fail to carry out any of the duties herein specified shall be fined by the local authorities in a sum not less than 5 or greater than 50 krone ($1.00 to $10.00).

Section 9. The technical examination of maize, and of foods in so far as they relate to the eradication of pellagra, shall be made by the agricultural experiment station at St. Michele, which was created by Section 25 of the law of the 16th of January, 1896, and the cost of such examination shall be borne by the pellagra fund.

Section 10. This law shall go into effect on the day of its publication.

Section 11. The execution of this law is intrusted to the minister of the interior, and in this must receive the assistance of his colleagues.

Dated Vienna, 14th of February, 1904.

FRANCIS JOSEPH, King.

ITALIAN LAW ON BAD MAIZE AND PELLAGRA.

Approved on 19th April, 1902.

Article 1. It is illegal to sell, to keep for sale, or administer under any form whatsoever to anyone.

(a) Maize that is immature, that is not well dried, that is mouldy, or is in any way spoiled, whether it be in the form of grain or of meal;

(b) Any of the products obtained from the said grain, or where such products were originally prepared from sound grain, but have later from any cause whatever become mouldy or spoiled.

Article 2. It is unlawful to introduce into the kingdom for the purpose of human consumption maize or any of its products which are spoiled or imperfect, or that which becomes so during transportation, or undergoes alterations of this character in the granaries where it is conserved.

Article 3. The transportation in the kingdom, the grinding and the utilization of maize and its derivatives that are spoiled or imperfect, for other use than human consumption, are under the jurisdiction of the magistrates or the local authorities, depending upon the regulations.

The lack of such authorization would expose the said products to immediate seizure, without prejudicing subsequent penal action.

Article 4. Violations of the three preceding articles shall be denounced to the judicial authorities, to the officials, and to the agents of the judicial police, and shall be purnished with fines of from 51 to 2,000 lire, $10 to $400.

The communal sanitary official shall not only denounce violations of the present law and any of its corresponding regulations of a penal character to the judicial authorities, but shall likewise inform the magistrate and the provincial physician.

Article 5. All fines collected from convicted violators of this law shall be turned in to the local treasurers and used for combatting and treating pellagra.

Article 6. In order that the law may be properly carried out, the sanitary officials and the sanitary police are empowered to visit all granaries of merchants that deal in maize or its products, and likewise all mills and factories where breads and pastes are made.

Article 7. Every case of pellagra, even of the most incipient character, shall be reported in the manner directed in articles 45 and 47 of the public health law of December 27, 1888, No. 5849.

Article 8. The communes where pellagra has been found to be epidemic are regulated after the manner specified in article 9, et seq., of the present law.

The carrying out of the articles just referred to is preceded by a decree of the magistrate, he having regard for the judgment of the provincial council of health. It becomes operative from the day of the official notification to the syndic, and must be published the same day.

Article 9. In communities where pellagra is declared endemic it becomes the duty of both the general and local authorities to compel the proper drying and conservation of maize and its products.

The rules and regulations necessary for the execution of this article and those that follow must be approved by the provincial administrative council, it giving heed to the provincial council of health, and, as respects the cultivation of the grain, to the agricultural committee and other agrarian institutions that may there legally exist.

Article 10. In communities that have been declared affected with pellagra, the magistrate, on approval of the provincial council of health, and, where it exists, the provincial pellagrological commission, is empowered to direct the construction or to buy one or more maize desiccators of a capacity corresponding to the local needs.

The rules for their operation will be prescribed in the regulations for carrying out the law.

The magistrate has equally the authority to order that the commune prepare a suitable station, approved by the local sanitary officials, which is hygienically adapted to the deposition and good conservation of Indian corn and of meal, where those who are not properly provided with suitable granaries may deposit and keep a quantity of this grain or its products which correspond to their needs.

In the establishment of desiccators and in the construction of granaries for the conservation of maize, the rules and the benefits of loans for aiding in works for the promotion of public health will be allowed according to the law of Feb. 8, 1901, No. 50.

Article 11. The communal council will make and keep for each community a list of the poor pellagrins whose families are unable to procure for them the necessary foods.

A curative regimen is prescribed for the pellagrous poor and is obligatory.

Article 12. The expense of carrying out articles 10, 11 and 12 is to be provided as follows:

(a) By private gifts.
(b) By aid from various public institutions.
(c) By fines from violation of Art. 5.
(d) By aid of the commune and of the province, one-half from each.
(e) By aid from the state.

Funds coming from the sources designated *a* and *b* shall be subtracted from the amount required of the commune.

Article 13. Where the subjects of the disease are poverty-striken and have not the quantity and quality of food necessary for their treatment, it shall be lawful for them to be received into general hospitals or those especially con-

ducted for the treatment of pellagrins (pellagrosari) or any other institutions of a similar kind.

Article 14. After the method and in the form determined by the regulations, either local or provincial committees, or provincial or communal pellagra commissions, may be created by ministerial decree, and it shall be their duty to aid the local authorities in the carrying out of the present law.

To such bodies will be particularly delegated special investigations for the prevention and cure of pellagra, as well as the introduction of better agricultural methods.

Article 15. In case of the hesitation or the refusal on the part of any commune to carry out the provisions of this law, the magistrate shall see to their execution as provided by the communal and provincial laws, but shall consult so far as necessary with the provincial administrative council.

Article 16. For the carrying out of the preventive measures, as well as those of a curative character, the commune and the provinces may unite together, depending upon local conditions and their convenience.

Article 17. There will be placed annually to the credit of the Minister of the Interior the sum of 100,000 lire for assisting the communes in the founding and carrying on of institutions for the treatment of pellagra.

An equal amount will also be placed to the credit of the Minister of Agriculture and Commerce for the encouragement and aid of such measures as will aid in the prevention of pellagra, whether they be of an economic character or directed toward bringing about improvement in agriculture.

Article 18. In communes which are declared affected by pellagra the Minister of Finance is authorized to have distributed gratuitously, for the exclusive use of poor pellagrins and their families, a sufficient quantity of salt under the direction of the sanitary officials.

The use of salt so distributed for other purposes than as just indicated will be punished according to the law of the 15th of June 1865, No. 6397.

Article 19. The carrying out of the present law shall be when necessary furthered and aided by royal decree on the request of the Ministers of the Interior and of Agriculture and Commerce, the Superior Council of Health concurring.

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EXPLANATION OF ILLUSTRATIONS.

Plate I.

Figs. 1, 2 and 3.—Showing inflammation of the mucosa of the cheeks, roof of mouth, tongue and soft palate.

Plate II.

Fig. 4.—Papular erythema of the backs of the hands somewhat resembling the lesions commonly encountered in pellagra.

Fig. 5.—Microscopic section of skin of the back of the hand in chronic pellagra.

Specimen fixed in Bensley's mercuric chloride solution, and stained with haematein and eosin.

A, Corneous layer. B, Malpighian layer. C, Corium. D, Sweat glands. E, Hair follicle. F, Swollen elastic tissue. G, Collections of collacin, which are seen as isolated masses, H, in cavities, I.

Fig. 6.—Artery from spleen. Technic as above.

Both the muscularis and adventitia generally show absence of nuclei, with fragmented remains of same; the tissues have largely undergone hyaline degeneration.

Plate III.

Figs. 7 and 8.—Semilunar ganglion. Tissues fixed in Bensley's solution, and stained in carbol-toluidine blue.

Fig. 7 under moderate magnification shows great masses of fibrous tissue, in which there are here and there found nerve cells, A.

Fig. 8 under higher powers shows nerve cells, A, some of which are fairly well preserved, while in other instances, B, the nuclei are displaced and are frequently destroyed,—the only remains being often a small basophilic structure, evidently the nucleolus; in some of the cells, as at C, there is much yellow pigment, and in others there is evidence of the so-called neurophagony, D.

Figs. 9 and 10.—Spinal cord. Tissues prepared by Weigerts method for myelin.

In Fig. 9 the pale areas indicate the location of sclerosis in the lateral and posterior columns, while in Fig. 10 the changes are in the anterior and posterior columns.

Figs. 11 and 12.—Ganglion cells from the cord. Tissues fixed in Bensley's solution, and stained in carbol-toluidine blue.

Fig. 11 shows a cell with a displaced and degenerate nucleus, while its protoplasm presents the peculiar hyaline change so often found in pellagra. Fig. 12 shows similar alterations, but here the nucleus has entirely disappeared, and the cell protoplasm contains numerous vacuoles. Both cells have lost their processes.

Plate IV.

Figs. 13, 14 and 15.—Cerebrum. Tissues prepared by the method of Herxheimer.

Fig. 13 shows in the perivascular lymph spaces great collections of fats or lipoids, here stained red, along the blood vessel at the left of the figure, and also nerve cells exhibiting similar changes.

Figs. 14 and 15.—Nerve cells under much higher powers showing fatty alterations.

Plate V.

Figs. 16-20.—From the central nervous system. Tissues fixed in Bensley's solution, and stained in carbol-toluidine blue.

Fig. 16 is a section from the cerebellum in which the granular layer is shown widely separated by fluids, B, from the molecular layers, A; there are degenerate cells of Purkinje at D, though many of these have disappeared.

Figs. 17 and 18 show hyaline cells of Purkinje in which the nuclei are gone, and the former cell contents only represented by a few basophilic bodies and pigment.

Figs. 19 and 20 represent hyaline cells from the cerebral cortex, which have lost all of their normal internal structures, as well as their processes; they contain vacuoles and pigment.

Plate VI.

Fig. 21.—Adrenal. Tissues fixed in Bensley's solution, and stained in haematin and eosin.

A, Capsule. B, Approximately normal glandular structure. C, Similar masses of epithelial cells the nuclei of which have for the most part disappeared. D, massed haemorrhage at the margin of the zona reticularis, and, E, small haemorrhages in the zona fasciculata.

Figs. 22 and 24.—Ganglion cells from cord. Tissues prepared by method of Bielschowsky.

In Fig. 22 the neurofibrils have disappeared, but in Fig. 24 they may be seen in the cell process.

Figs. 23 and 25 are from nerve cells of the cerebral cortex. Tissues prepared by the method of Bielschowsky.

In neither of these are there remains of the neurofibrils.

Plate VII.

Types of drying ovens for conserving maize.

PLATE I.

Fig. 1.

Fig. 2.

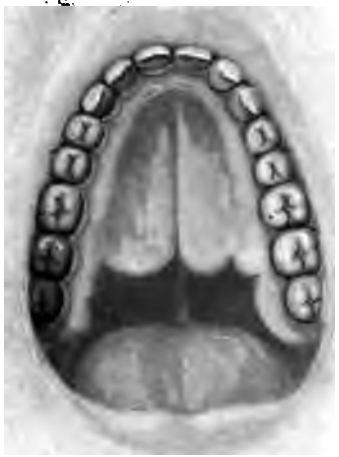


Fig. 3.

PLATE II.

Fig. 4.

Fig. 5.

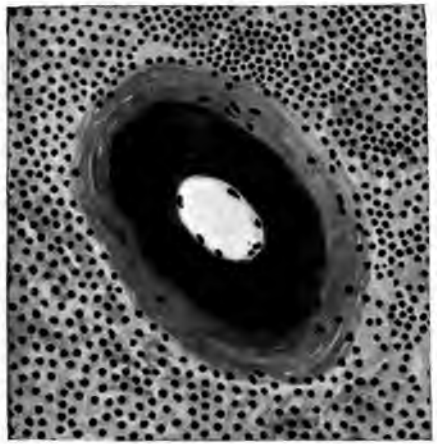
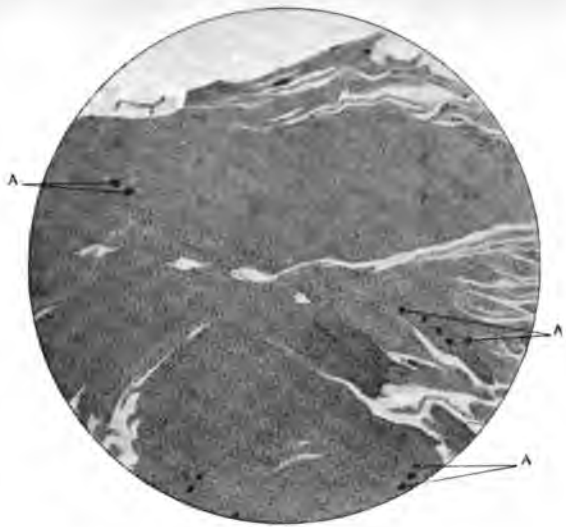


Fig. 6.

PLATE III.



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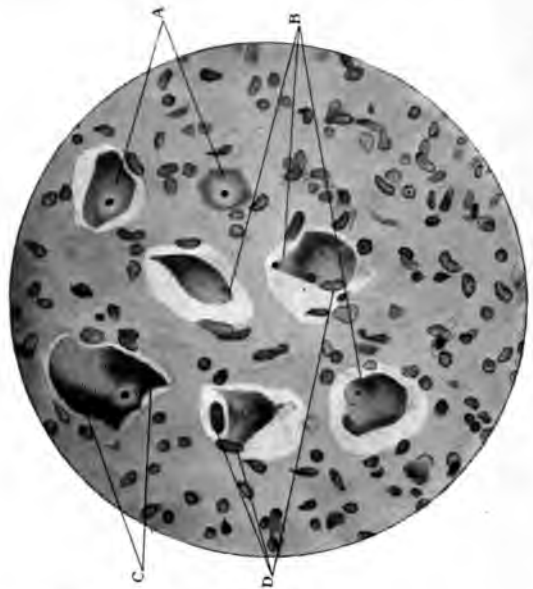

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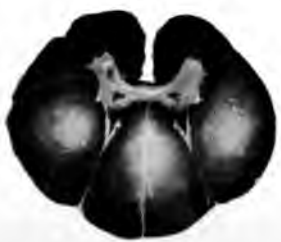


Fig. 9.

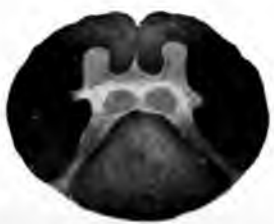


Fig. 10.

Fig. 11.

Fig. 12.

PLATE IV.

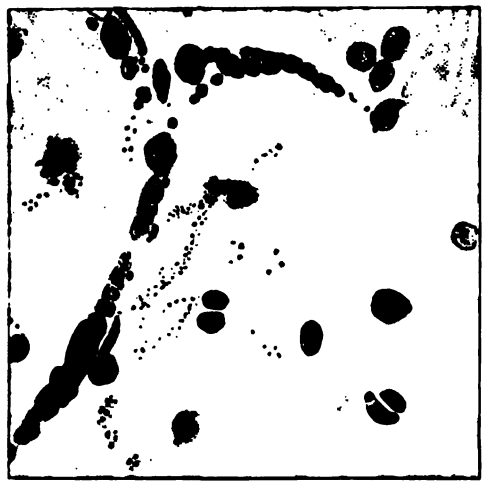


Fig. 13.

Fig. 14.

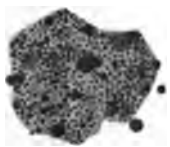


Fig. 15.

PLATE V.

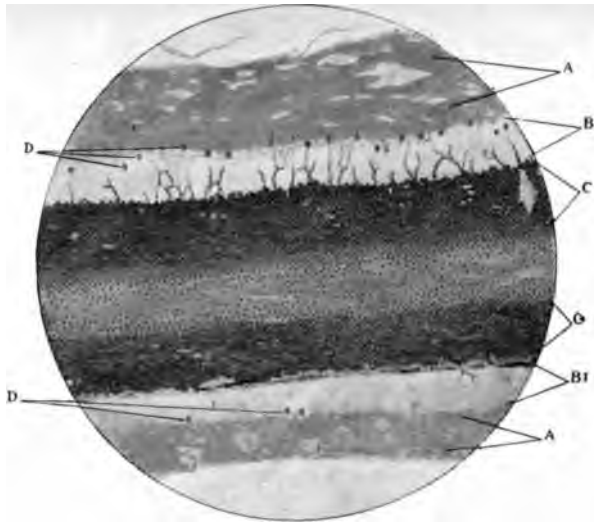


Fig. 16.

Fig. 17.

Fig. 18.

Fig. 19.

Fig. 20.

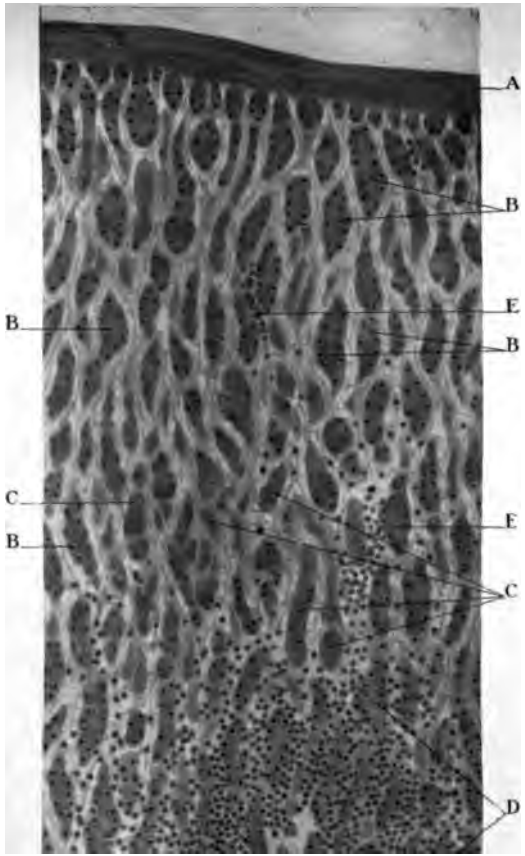


Fig. 22.

Fig. 23.

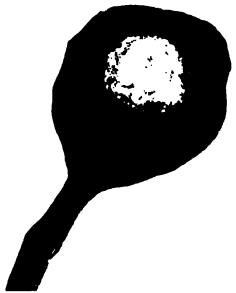


Fig. 25.

Fig 1

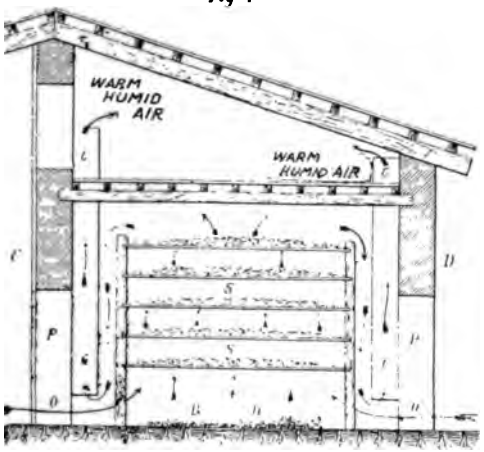


Fig 3

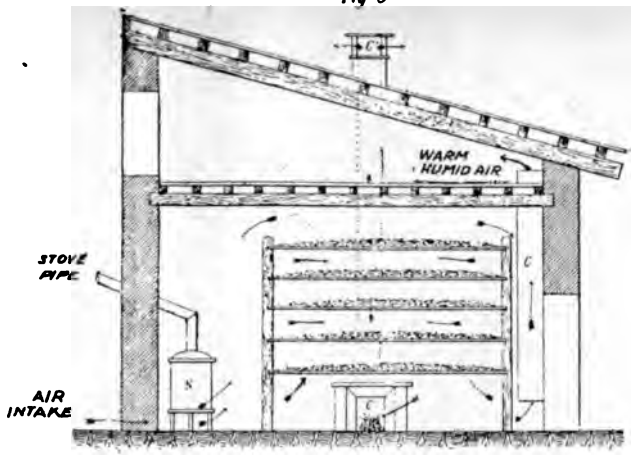


Fig 5

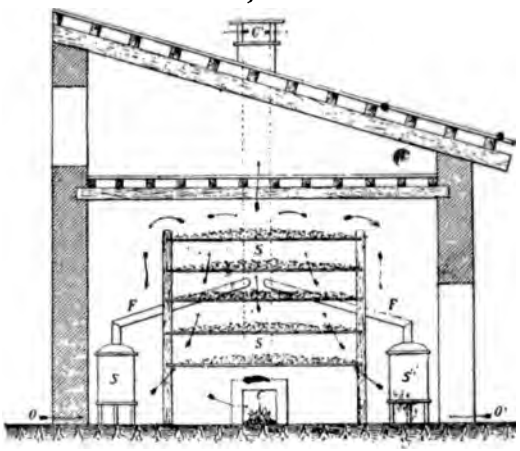


Fig 2

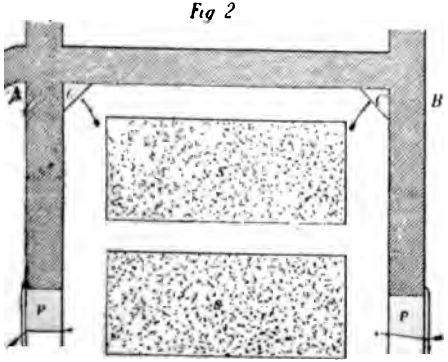


Fig 4

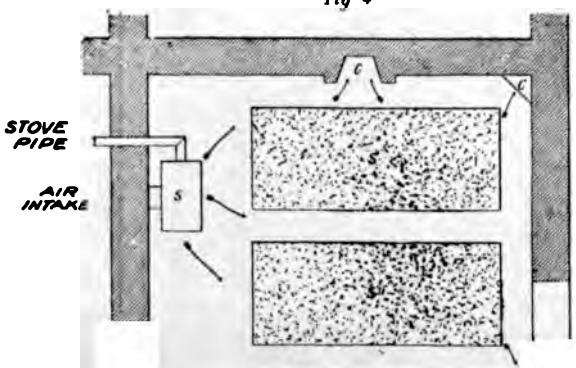
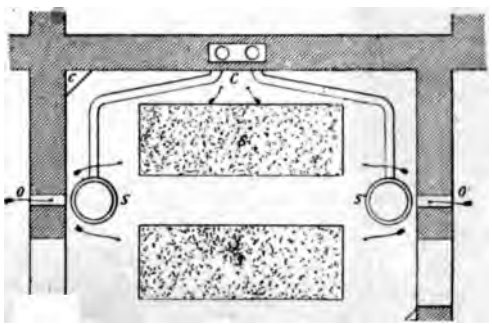


Fig 6



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